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Part II

Department of Health, Education, and Welfare

Food and Drug Administration

Viral and Rickettsial Vaccines; Proposed Implementation of Efficacy Review

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

21 CFR Parts 601 and 630

[Docket No. 78N-0100]

Viral and Rickettsial Vaccines; Proposed Implementation of Efficacy Review

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations in response to the report and recommendations of the Panel of Review of Viral Vaccines and Rickettsial Vaccines. The Panel reviewed the safety, efficacy, and labeling of viral and rickettsial vaccines and human and equine immune serum globulins. On the basis of the Panel's findings and recommendations, the Commissioner of Food and Drugs is proposing to classify those products in Category I (safe, effective, and not misbranded) and Category IIIA (on the market during futher studies in support of effectiveness) and is inviting comments and the submission of additional data on the status of these products.

The Commissioner is also announcing his conclusions as to those products which are in Category II (unsafe, ineffective, or misbranded) and Category IIIB (off the market pending completion of studies permitting a determination of effectiveness). In the near future, the Commissioner will publish a notice of opportunity for a hearing (NOH) to revoke the licenses for products in Categories II and IIIB. Comments and additional data will be requested in the NOH.

DATES: Comments on the classification of products into Category I and IIIA and on proposed amendments to the biologics regulations should be submitted on or before July 14, 1980. Comments on the confidentiality of data submitted ror review by the Panel should be submitted on or before May 15, 1980.

ADDRESSES: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Steven F. Falter, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of February 13, 1973 (38 FR 4319), the Commissioner issued § 601.25 (21 CFR 601.25) concerning procedures for the review of the safety, effectiveness, and labeling of biological products licensed prior to July 1, 1972. Under a redesignation of panel assignments published in the **Federal Register** of June 19, 1974 (39 FR 21176), the biological products reviewed were assigned to one of the following categories: (a) bacterial vaccines and bacterial antigens with "no U.S. standard of potency," (b) bacterial vaccines and toxoids with standards of potency, (c) viral vaccines and rickettsial vaccines, (d) allergenic extracts, (e) skin test antigens, or (f) blood and blood derivatives.

Under § 601.25, the Commissioner assigned responsibility for the initial review of each of the biological product categories to a separate independent advisory review panel consisting of qualified experts to ensure objectivity of the review and public confidence in the use of these products. Each panel was charged with preparing an advisory report to the Commissioner which was to: (1) evaluate the safety and effectiveness of the biological product, (2) review the labeling of the biological product, and (3) advise him on which biologcal products under review are safe, effective, and not misbranded. The advisory report includes a statement classifying products into one of three categories.

Category I designates those biological products determined by the panel to be safe, effective, and not misbranded. The panel's statement may include any condition relating to active components, labeling, tests required prior to release of batches, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

Category II designates those biological products determined by the panel to be unsafe or ineffective or to be misbranded.

Category III designates those biological products determined by the Panel not to fall within either Category I or II on the basis of its conclusion that the available data are insufficient for classification and for which further testing is therefore required. Those biological products in Category III for which continued licensing, manufacturing, and marketing are recommended are designated as Category IIIA. Those biological products in Category III for which the suspension of their license is recommended are designated as Category IIIB. The recommendations for either Category IIIA or IIIB are based on assessment of the present evidence of safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time, while questions raised concerning the products are being resolved by further study.

Because of a recent Federal court decision involving the review and classification of over-the-counter drugs, the agency has reevaluated the legal status of on-going product review procedures. It is FDA's conclusion that the biologics' review Category IIIA designation is proper and is unaffected by the ruling applicable to OTC drugs.

The case, *Cutler* v. *Kennedy*, challenged the propriety of the OTC classification Category III, which authorized the continued marketing of OTC drugs that had been found to be not generally recognized as safe and effective and thus which were new drugs as defined by the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(p), but for which there were no effective new drug applications as required by 21 U.S.C. 355. If a drug is not a new drug because it is generally recognized as safe and effective, no such approval is required.

On July 16, 1979, the United States District Court for the District of Columbia concluded that to the extent that the OTC Category III authorized the marketing of drugs that are new drugs but yet unapproved, that interim status was illegal. The Court ruled that the new drug provisions of the Federal Food, Drug, and Cosmetic Act created a statutory benchmark and that no drug failing to meet the statutory criteria could be classified otherwise while further data were being developed.

The regulations governing the biologics review (21 CFR 601.25) also provide for a classification, Category IIIA, to designate those products for which safety and effectiveness data are incomplete but which remain on the market while further data are developed. However, the biologics under review have been licensed under the Public Health Service Act, 42 U.S.C. 262. The purpose of the review is not to establish, for the first time, the marketing status of a product, as is the purpose of the OTC review, but rather to reaffirm or question, based upon current scientific standards, the data upon which the license is based. Classification of a biologic in biologics Category IIIA does not reflect a finding that a product cannot, as a matter of law, be licensed or that it is not exempt from the licensure requirement, but rather that the data are insufficient to recommend revoking the existing license

or that the data supporting the license should be supplmented. In this respect a Category IIIA biologic is in a regulatory status analogous to that of an interim food additive. See 21 CFR 180.1. Licensed biologicals are not subject to the new drug provisions of the Federal Food, Drug, and Cosmetic Act. See 21 CFR 310.4. The question of their being "new" and thus requiring prior FDA approval or "old" (generally recognized as safe and effective) and thus not subject to prior review is not at issue. All biologics must be licensed whether they are generally recognized as safe and effective or not.

In the **Federal Register** of February 28, 1973 (38 FR 5359), the Commissioner requested data and information regarding viral vaccines and rickettsial vaccines. Additional data and information regarding the safety and effectiveness of related immune globulins and sera were requested in the **Federal Register** of June 19, 1974 (38 FR 21176).

Some concern has been expressed that information submitted to FDA under § 601.25 will become public information. Data and information submitted in response to the February 28, 1973 and June 19, 1974 notices and falling within the provisions of 5 U.S.C. 552(b), 18 U.S.C. 1905, or 21 U.S.C. 331(j) have been handled as confidential. However, with the publication of this proposed implementation and the Panel's findings, such data and information will, under § 601.25(b)(2), be made publicly available after May 15, 1980, and may be viewed at the office of the Hearing Clerk, except to the extent that the person submitting the data and information demonstrates that it still falls within the confidentiality provisions of one or more of the above statutes. Accordingly, comments concerning confidentiality should be submitted on or before May 15, 1980.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectivenes, and labeling of viral vaccines, rickettsial vaccines, and related immune globulins and antiserum:

Panel chairman, Saul Krugman, M.D., Professor, Department of Pediatrics, New York University School of Medicine, New York, NY 10016;

John P. Fox, M.D., Professor, Department of Epidemiology, University of Washington, Seattle, WA 98105;

William S. Jordan, Jr., M.D., Professor, Department of Community Medicine, University of Kentucky School of Medicine, Lexington, KY 40506 (since September 1, 1976, Director, Microbiology and Infectious Diseases Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20205);

Edwin H. Lennette, M.D., Ph.D., Chief Viral and Rickettsial Diseases Laboratory, California Department of Health, Berkeley, CA 94704;

June E. Osborn, M.D., Professor of Pediatrics and Medical Microbiology, Associate Dean of the Graduate School, University of Wisconsin, Madison, WI 53706;

Kenneth McIntosh, M.D., Professor of Pediatrics, University of Colorado Medical Center, Denver, CO 80262;

Wade P. Parks, M.D., Ph.D., Head, Viral Carcinogenesis Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20205 (resigned from Panel June 30, 1976).

The Panel was convened on July 2, 1973 in an organizational meeting. Working meetings were held: July 2, August 30–31, October 29–30, December 17–18, 1973; February 6–7, April 2–3, June 17, September 6–7, November 4–5, 1974; January 6, February 10–11, March 12–13, April 10–11, July 7–9, December 18–19, 1975; February 10–11, June 22–24, 1976; January 24, October 3–4, 1977; and January 23–25, 1978.

Two nonvoting liaison representatives served on the Panel. W. Palmer Dearing, M.D., nominated by the Consumer Federation of America, served as the consumer representative. John Adams, Ph.D., of the Pharmaceutical Manufacturers Association, nominated by a number of producers with products under review by the Panel, served as the industry representative. Karl Bambach, Ph.D, substituted for Dr. Adams during his absences. Morris Schaeffer, M.D., Ph.D., participated in the Panel meetings in his capacity as Director of the Office of Efficacy Review, Bureau of Biologics, FDA. Jack Gertzog, Deputy Director, Office of Efficacy Review, Bureau of Biologics, FDA, served as Executive Secretary of the Panel.

In addition, the Panel considered the advice of the following consultants:

Samuel L. Katz, M.D.
David T. Karzon, M.D.
Edwin D. Kilbourne, M.D.

Over 250 persons requested an opportunity or were otherwise invited to appear before the Panel and present their views on one or more of the vaccines and related matters. Every person who requested an opportunity was heard by the Panel. The names of these persons are on file with the Hearing Clerk.

The Panel on Review of Viral Vaccines and Rickettsial Vaccines evaluated all data submitted for the following vaccines and other related products:

Table 1—*Licensed Vaccines Considered by the Panel* [1]

Manufacturer	Product
Parke, Davis & Co	Adenovirus Vaccine.
	Adenovirus and Influenza Virus Vaccines, Combined, Aluminum Phosphate Adsorbed.
Eli Lilly & Co	Influenza Virus Vaccine.
Lederle Laboratories Division, American Cyanamid Co.	Influenza Virus Vaccine.
Merrell-National Laboratories, Division of Richardson-Merrell, Inc..	Influenza Virus Vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Influenza Virus Vaccine.
Parke, Davis & Co	Influenza Virus Vaccine.
Wyeth Laboratories, Inc	Influenza Virus Vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Measles, Mumps and Rubella Virus Vaccine, Live.
	Measles and Rubella Virus Vaccine, Live.
	Measles-Smallpox Vaccine, Live.
Dow Chemical Co	Measles Virus Vaccine, Live, Attenuated.
Lederle Laboratories Division, American Cyanamid Co.	Measles Virus Vaccine, Live, Attenuated.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Measles Virus, Vaccine, Live, Attenuated.
Eli Lilly & Co	Mumps Vaccine.
Lederle Laboratories Division, American Cyanamid Co.	Mumps Vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Mumps Virus Vaccine, Live.
Connaught Laboratories, Ltd	Poliomyelitis Vaccine.
Cutter Laboratories, Inc.	Poliomyelitis Vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Poliomyelitis Vaccine.
Parke, Davis & Co	Poliomyelitis Vaccine.
	Poliomyelitis Vaccine, Adsorbed.
Lederle Laboratories Division, American Cyanamid Co.	Poliovirus Vaccine, Live, Oral Trivalent, Type 1, Type 2, and Type 3.
Pfizer, Ltd	Poliovirus Vaccine, Live, Oral, Trivalent.
	Poliovirus Vaccine, Live, Oral, Type 1.
	Poliovirus Vaccine, Live, Oral, Type 2.
	Poliovirus Vaccine, Live, Oral, Type 3.
Wyeth Laboratories, Inc.	Poliovirus Vaccine, Live, Oral, Trivalent.
	Poliovirus Vaccine, Live, Oral, Type 1.
	Poliovirus Vaccine, Live, Oral, Type 2.
	Poliovirus Vaccine, Live, Oral, Type 3.
Eli Lilly & Co	Rabies Vaccine.
Lederle Laboratories Division, American Cyanamid Co.	Rocky Mountain Spotted Fever Vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Rubella and Mumps Virus Vaccine, Live.
	Rubella Virus Vaccine, Live.
Recherche et Industrie Therapeutiges, S.A. (Smith Kline and French).	Rubella Virus Vaccine, Live.
Division of Biological Products, Bureau of Laboratories, Michigan Department of Public Health.	Smallpox Vaccine.
Connaught Laboratories, Ltd	Smallpox Vaccine.
Lederle Laboratories Division, American Cyanamid Co.	Smallpox Vaccine.
Massachusetts Public Health Biologic Laboratories.	Smallpox Vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Smallpox Vaccine.
Merrell-National Laboratories, Division of Richardson-Merrell, Inc..	Smallpox Vaccine.
Wyeth Laboratories, Inc	Smallpox Vaccine.
Eli Lilly & Co	Typhus Vaccine.
Lederle Laboratories Division, American Cyanamid Co.	Typhus Vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Typhus Vaccine.

Table 1—*Licensed Vaccines Considered by the Panel*[1]—Continued

Manufacturer	Product
Merrell-National Laboratories, Division of Richardson-Merrell, Inc.	Yellow Fever Vaccine.

[1] Only biological products that have been licensed prior to July 1, 1972, are reviewed in this report.

Table 2—*Licensed Antiserum and Human Immune Globulin Preparations*[1]

Manufacturer	Product
Istituto Sieroterapico Vaccinogeno Toscano, "Sclavo".	Antirabies Serum.
Lederle Laboratories Division, American Cyanamid Co.	Antirabies Serum.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Immune Globulin (Human), Pepsin-Modified.
Abbott Laboratories	Immune Serum Globulin (Human).
Armour Pharmaceutical Co.	Immune Serum Globulin (Human).
Division of Biologic Products, Bureau of Laboratories, Michigan Department of Public Health.	Immune Serum Globulin (Human).
Cutter Laboratories, Inc	Immune Serum Globulin (Human).
Dow Chemical Co	Immune Serum Globulin (Human).
E. R. Squibb & Sons, Inc	Immune Serum Globulin (Human).
Lederle Laboratories Division, American Cyanamid Co.	Immune Serum Globulin (Human).
Massachusetts Public Health Biologic Laboratories.	Immune Serum Globulin (Human).
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Immune Serum Globulin (Human).
North American Biologicals, Inc.	Immune Serum Globulin (Human).
Osterreichisches Institut fur Haemoderivate G.m.b.H.	Immune Serum Globulin (Human).
Parke, Davis & Co	Immune Serum Globulin (Human).
Travenol Laboratories, Inc., Hyland Division.	Immune Serum Globulin (Human).
Wyeth Laboratories, Inc	Immune Serum Globulin (Human).
Lederle Laboratories Division, American Cyanamid Co.	Measles Immune Globulin.
Parke, Davis & Co	Measles Immune Globulin.
Cutter Laboratories, Inc	Mumps Immune Globulin (Human)
Travenol Laboratories, Inc., Hyland Division.	Mumps Immune Globulin (Human).
Travenol Laboratories, Inc., Hyland Division.	Vaccinia Immune Globulin (Human).

[1] Only biological products that have been licensed prior to July 1, 1972, are reviewed in this report.

The advisory Panel appointed to review data and information concerning safety, effectiveness, and labeling of viral and rickettsial vaccines has completed their review as follows:

Basis of Evaluation

The development of various viral vaccines has had a profound influence on the course and history of preventive medicine during the past two centuries. The necessary technology is now available to prepare safe, potent, and highly effective vaccines for the prevention of smallpox, poliomyelitis, measles, mumps, rubella, and other viral diseases. The extensive use of these vaccines is responsible in great part for the substantial decline in the morbidity and mortality of infectious diseases.

The terms "safety," "potency," and "effectiveness" are relative, not absolute. The evaluation of these terms and their application to the assessment of a licensed vaccine is based, in great part, on the risk-benefit assessment of the product in question. The importance of this position was highlighted by Sir Graham Wilson when he stated:

> It is fair to conclude that most of the well-known protective immunological agents that we use do a great deal more good than harm. The complications and accidents for which they are from time to time responsible must be looked upon as the price we pay for the protection these agents confer upon us. There is no insurance without a premium. Our business is to provide a greater and more comprehensive insurance and to diminish the size of the premium.

The role of viral vaccines in promoting the health and welfare of mankind may be illustrated by a brief historical review of three vaccines which have had a notable impact in reducing the high morbidity prevalent during the prevaccination era.

1. *Smallpox.* The efficacy of vaccination for the prevention of smallpox was well established at the beginning of the 19th century. In 1796, Edward Jenner performed the first human-to-human vaccination with pustular material obtained from the cowpox lesion of a milkmaid's hand. A typical pox lesion developed on the arm of the boy who was inoculated. Some 2 month later, the boy was shown to be immune to reinoculation with pustular material from an active case of smallpox. Jenner extended these studies and showed that cowpox, a mild disease, was protective against smallpox. His historic observations were published in 1798 and 2 years later his findings were confirmed by Benjamin Waterhouse in the United States.

However, the availability of an effective vaccine did not eradicate smallpox and it remained a serious problem more than a century later. During the 10-year period from 1920 to 1930, there were more than 530,000 reported cases and 4,790 smallpox deaths in the United States. The acceptance of vaccination as a routine public health practice resulted in a decline in the number of smallpox cases in the United States from 110,672 in 1920 to 40,280 in 1925; 15,000 in 1938; 56 in 1948; and 0 in 1954. During the past 20 years, there has been not one confirmed case of smallpox reported in the United States.

The eradication of smallpox from most countries of the world in the 1970's has been an extraordinary achievement. The impact of Jenner's great contribution in incalculable. When he performed his first vaccination in 1796, about 45,000 deaths were caused by smallpox in Britain each year. Moreover, of all reported deaths, one in every five was due to this disease, and during the 18th century smallpox was responsible for the death of more than 60 million people in the world.

2. *Poliomyelitis.* The dramatic decline in the incidence of poliomyelitis in the United States is a direct result of the polio-vaccine program initiated in 1955. In 1954, there were 38,000 reported cases of poliomyelitis, of which 18,500 were paralytic. In 1975, there were only 5 paralytic cases, an alltime low since official reporting of the disease was initiated in 1912. Since 1954, more than 400 million doses of inactivated poliovirus vaccine (Salk) have been distributed in the United States. In addition, since 1961 more than 400 million doses of live, attenuated, poliovirus (Savin) have been used in extensive community-wide and routine immunization programs.

Inactivated poliovirus vaccine was the first safe and effective vaccine to be used for the prevention of poliomyelitis. Despite its excellent record, it did have limitations, namely, the vaccine's antigenic potency was variable and repeated inoculations were necessary to maintain antibody levels which declined rather rapidly (Refs. 1 through 10).

Live attenuated poliovirus has been used extensively throughout the world as a vaccine. Its effectiveness and safety have been well established. It is given orally; it is antigenically potent; and a single dose is followed by a rapid antibody response. Its capacity to produce intestinal resistance to reinfection has been responsible for its capacity to abort epidemics of poliomyelitis. The oral vaccine has been as effective, more acceptable, and more convenient to administer than an injectable vaccine.

3. *Measles.* Measles has been recognized as a disease for more than 11 centuries. It was first described in 850 A.D. by Rhazes, an Arabian physician. This universal disease, occurring on all continents and in all people, has had a major impact on the history and destiny of many nations. For example, Louis XV, King of France, became heir to the French crown after measles killed his brother, mother, and father. During an epidemic in the Fiji Islands in 1875, approximately 20,000 people died of measles, a loss of about one-fifth of the native population. The disease had a tremendous impact on the American Civil War, affecting 75,000 troops and causing approximately 5,000 deaths. Even as late as World War I it was an important cause of military casualties. During 1918 and 1919, 90,000 soldiers

caught the disease and more than 2,000 died. The advent of antibiotics and gamma globulin after World War II was followed by a significant decline in the bacterial complications of measles. However, despite a remarkable decrease in the mortality rate, measles continued to be an uncontrollable disease which attacked most children before adolescence.

The most significant advance toward the control of measles occurred in 1954, more than 1,100 years after the disease was recognized. In that year John F. Enders and his colleagues first isolated a strain of measles virus, later known as the Edmonston Strain. They later succeeded in attenuating the virus. In March 1963, after 9 years of carefully controlled trials by many investigators, a live attenuated measles virus vaccine, Edmonston Strain, was licensed for use in the United States. A further attenuated strain of live measles virus, the Schwarz Strain, was subsequently licensed as a vaccine in February 1965. The use of more than 60 million doses of vaccine during the past 10 years has been followed by a dramatic decline in the incidence of measles and measles encephalitis in the United States (See Figs. A–1 and A–2).

The number of reported cases of measles has declined from approximately 500,000 per year before licensing the vaccine in 1963 to less than 50,000 cases since 1972. The number of reported cases of measles encephalitis has declined progressively from approximately 300 prior to 1963 to an alltime low of 14 in 1974.

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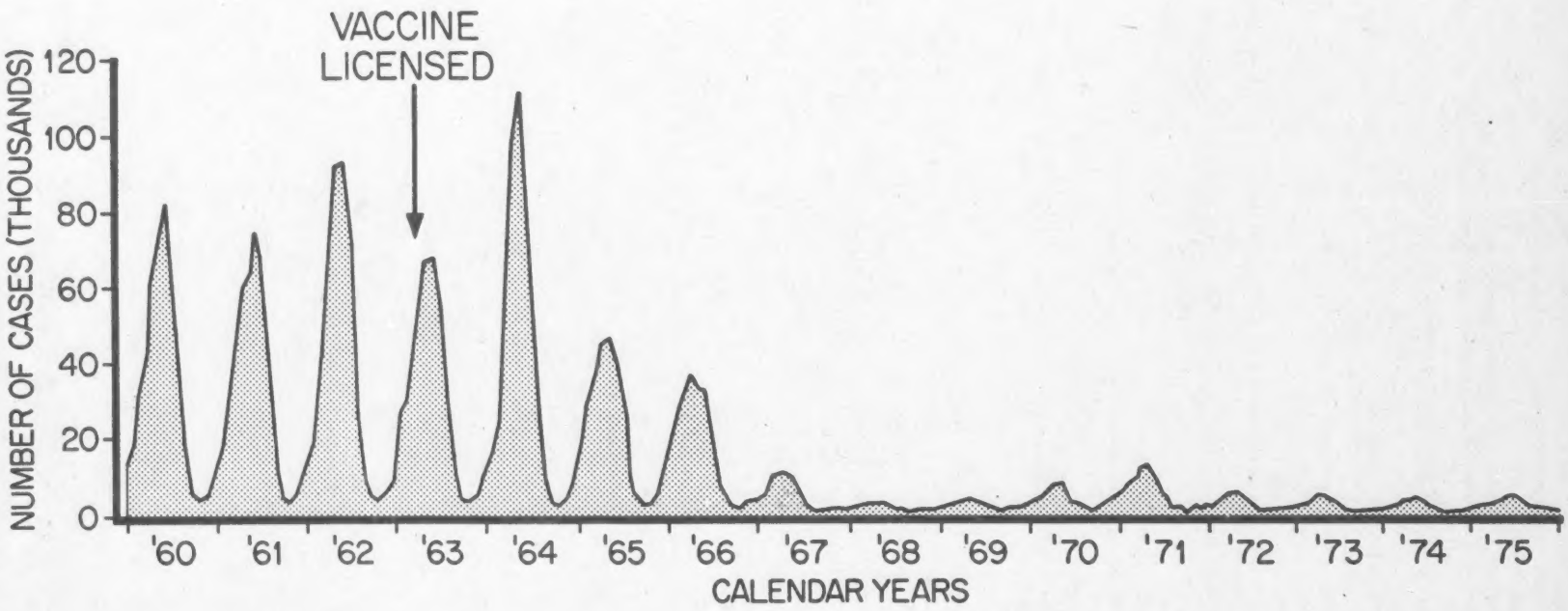
Figure A-1

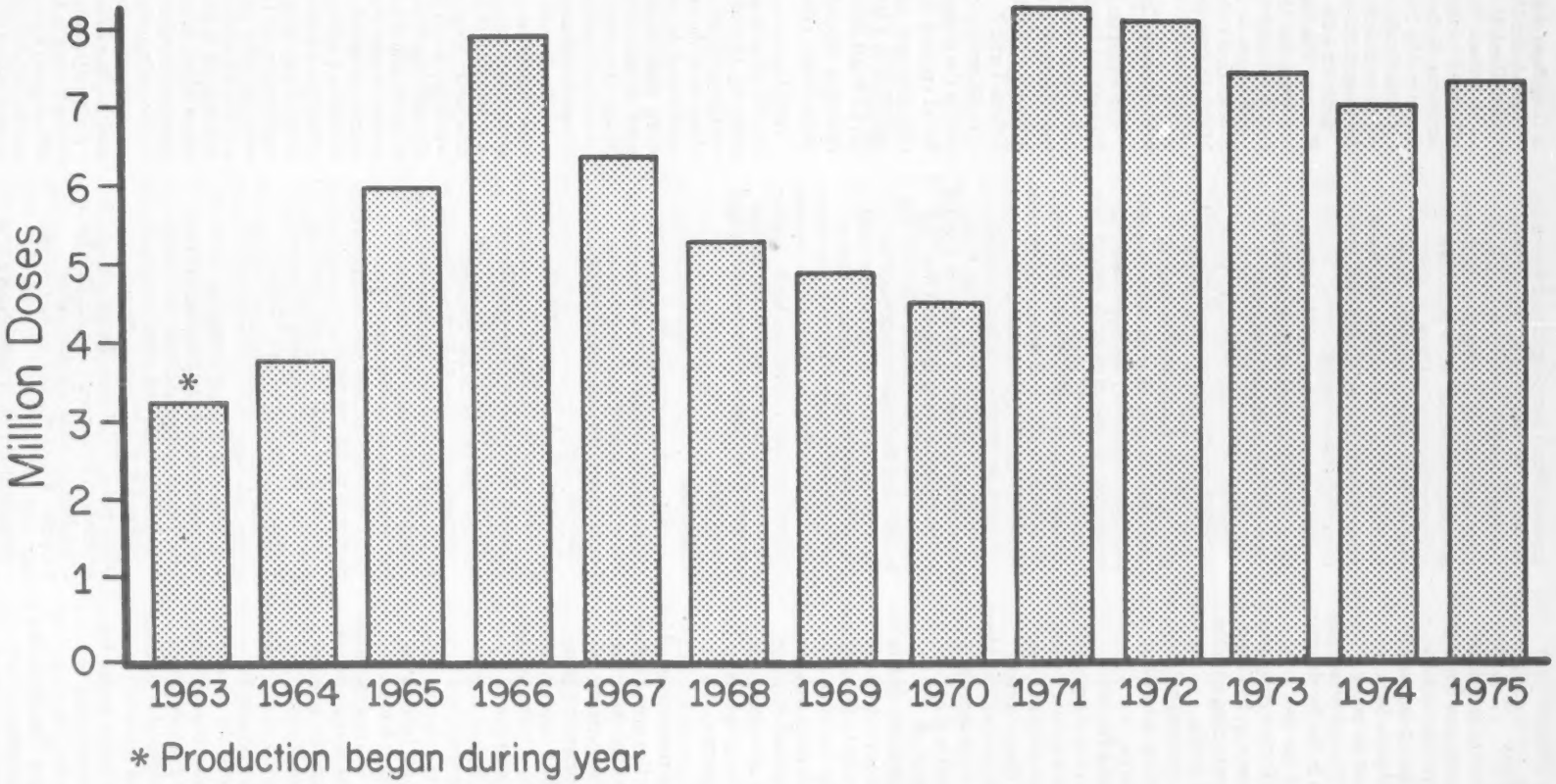
REPORTED CASES OF MEASLES BY FOUR-WEEK PERIODS UNITED STATES, 1960-1975



Source: Center for Disease Control

Figure A-2

Net Doses of Live Measles Vaccine Distributed United States 1963-1975



Source: Center for Disease Control

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Risk and Responsibilities

The development and subsequent licensing of effective vaccines for the prevention of poliomyelitis, measles, mumps, and rubella during the past 2 decades stem, in great part, from important contributions by many investigators in the United States. Thus, this country has been in the forefront in its support of research for the prevention of these infectious diseases. The United States, however, has been backward in its failure to deal with the important problem of public responsibility for the minimal but unavoidable risks associated with immunization procedures.

It is well-known that adverse reactions and even severe complications may occur in rare circumstances, even when vaccine has been prepared and used in accordance with accepted regulations and recommendations. Most reactions of this type represent an unusual and unpredictable host response. The occurrence of postvaccinal encephalitis is a classic example. Also, coincidental disease totally unrelated causally to the vaccine is bound to occur under the laws of probability. Given such circumstances, it is difficult to place responsibility and determine the validity of liability and malpractice suits against physicians and claims for damages against manufacturers.

Since immunizations recommended by national health authorities are of benefit not only for the recipient of the vaccine but for the community in general, several European countries and Japan have established a public compensation system under which the government has accepted responsibility for the recognized hazards of immunization.

In assessing liability, the responsibilities of manufacturer, physician, and State must be clearly defined. The manufacturer has two major responsibilities, i.e., to ensure that each batch of vaccine is manufactured and tested in strict accordance with regulations, and to include in the package insert for physicians a careful description of the risks that may be associated with the use of the vaccine in question. Medical personnel are obligated to inform the prospective vaccinee of any known possible risk.

In contrast with other types of prescription drugs, the major quantities of vaccines used are provided in connection with public health immunization campaigns. The State and Federal governments assume responsibilities for planning, funding, and implementing public health immunization campaigns and for licensing the vaccines which may be used legally. The government should also assume a further responsibility to provide compensation to persons suffering damage because of rare untoward reactions resulting from administration of vaccines which are properly manufactured, labeled, and correctly administered.

Sir Graham Wilson concluded his book, "The Hazards of Immunization," with the following commentary:

> Vaccines, of one sort of another, have conferred immense benefit on mankind but, like aeroplanes and motor-cars, they have their dangers. My intention has been to provide information on these dangers in the belief that, unless they are known and recognized, the task of guarding against them is bound from time to time to meet with unexpected and possibly disastrous failures. Manufacturers entrusted with the preparation of immunological products must, in particular, be careful to maintain eternal vigilance. A single slip may be disastrous. Over-confidence must at all costs be avoided. St. Paul issued a warning against this: "Let him that thinketh he standeth take heed lest he fall"; and Shakespeare expressed the same thought in even stronger terms: "And you all know security Is mortals' chiefest enemy". It is for us, and for those who come after us, to see that the sword which vaccines and antisera have put into our hands is never allowed to tarnish through over-confidence, negligence, carelessness, or want of foresight on our part.

References

(1) Batson, R., A. Christie, D. Turner, M. Michal, and J. H. Barrick, "The Persistence of Poliomyelitis Antibodies After Primary Immunization of Young Infants," *Pediatrics*, 23:550–552, 1959.

(2) Batson, R., A. Christie, W. J. Cheatham, M. Michal, and G. W. Sleight, III., "Antibody Response and Survival Following Booster Injections of Poliomyelitis (Killed-Virus) Vaccine," *Pediatrics*, 29:116–120, 1962.

(3) Bottiger, M., "Antibody Stimulation in Individuals Without Demonstrable Poliovirus Antibodies Following a Fifth Injection of Inactivated Poliovirus Vaccine," *Acta Pathologica et Microbiologica Scandinavica, Section B*, 81:795–798, 1973.

(4) Lepow, M. L., D. H. Carver, and F. C. Robbins, "Serologic Response of Nonimmune Subjects to Commercial Salk Vaccine," *American Journal of Diseases of Children*, 102:803–811, 1962.

(5) Brown, G. C. and J. A. Napier, "Serologic Status of Children Four (4) Years After Poliomyelitis Field Trial," *Journal of Immunology*, 84:463–468, 1960.

(6) Kendall, E. J. C., T. S. L. Beswick, A. Miller, and J. O'H. Tobin, "Persistence of Antibody in Adolescents and Adults After a Third, Booster, Dose of Poliomyelitis Vaccine," *British Medical Journal*, 1:1689–1691, 1960.

(7) Kendall, E. J. C., A. Miller, and J. O'H Tobin, "Further Observations on the Persistence of Antibody in Adolescents After a Third Dose of Killed Poliomyelitis Vaccine, *British Medical Journal*, 1:176–177, 1961.

(8) Gelfand, H. M., D. R. LeBlance, J. P. Fox, and L. Potash, "Studies on the Development of Natural Immunity to Poliomyelitis in Louisiana, III, the Seroligic Response to Commercially Produced 'Salk Vaccine' of Children Totally or Partially Susceptible to Poliovirus Infection," *American Journal of Hygiene*, 70:303–311, 1959.

(9) Smith, J. W., J. N. Lee, and W. B. Fletcher, "The Response to Oral Poliovaccine in Persons Age 16–18, years," *Journal of Hygiene (Cambridge)*. 76:235–247, 1976.

(10) Kogon, A., I. Spigland, L. E. Back, and J. P. Fox, "Oral Poliovirus Vaccination in Middle Income Families," *American Journal of Epidemiology*, 82:14–26, 1965.

Introductory Comments

The Panel on Review of Viral and Rickettsial Vaccines evaluated all data submitted in support of the licensure of the vaccines, antisera, and human immune globulin preparations listed in Tables 1 and 2.

In its review of the submitted data and in the preparation of its report, the Panel applied the definitions of safety, effectiveness, and labeling which are specified in § 601.25(d) (1) through (5) (21 CFR 601.25(d) (1) through (5)) of the biologics regulations governing the new procedures. These regulations state:

> (1) Safety means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the biological product is safe under the prescribed conditions of use, including results of significant human experience during use.
>
> (2) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.111(a) (5)(ii) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during

marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(3) The benefit-to-risk ratio of a biological product shall be considered in determining safety and effectiveness.

(4) A biological product may combine two or more safe and effective active components: (i) When each active component makes a contribution to the claimed effect or effects; (ii) when combining of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components; and (iii) if the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent preventive therapy or treatment for a significant proportion of the target population.

(5) Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall comply with Section 351 of the Public Health Service Act and sections 502 and 503 of the Federal Food, Drug, and Cosmetic Act, and in particular with the applicable requirements of §§ 610.60 through 610.65 and Subpart D of Part 201 of this chapter.

These definitions are elaborated upon as appropriate within the generic review for each vaccine.

After completing a product-by-product review, the Panel assigned each product to one of the following three categories:

Category I. Biological products determined to be safe and effective and specifying conditions under which they would not be misbranded.

Category II. Biological products determined to be unsafe or ineffective or misbranded.

Category III. Biological products determined not to fall within either Category I or II on the basis of the Panel's conclusion that the available data are insufficient to classify such products, and for which further testing is therefore required. For those products judged to be in Category III, the Panel was asked to recommend whether the license for the product should be retained (IIIA) or revoked (IIIB), while adequate data concerning safety, effectiveness and potency were being generated under controlled conditions.

The report which follows includes the basis for the Panel's recommendations and the details of both generic review of each type of vaccine and an individual review of each licensed product. If there is only a single manufacturer for a product, the generic considerations are included within the review of such single products. In some instances, the generic reviews recommend that additional studies be conducted on vaccines found by the Panel to be safe and effective (Category I). While the charge to the Panel by the Commissioner of Food and Drugs did not specifically ask for such recommendations in relations to safe and effective (Category I) products, the Panel considers such studies as appropriate for assessment of the benefit-to-risk factors which the Panel was asked to consider. With respect to its recommendations for additional studies for Category I products, the Panel believes that the state of the art and the benefit/risk assessments will both benefit by these recommendations.

As a preamble to the generic and individual product reviews, the Panel has prepared the following statement which discusses the overall basic principles and considerations relating to viral and rickettsial vaccines.

Basic Concepts of Immunity to Viral and Rickettsial Infections

Natural infection with virus and rickettsiae, with the important exception of respiratory viruses, is followed by solid and long lasting immunity which protects against clinical disease and reinfection, the latter to a variable extent. For most contact-transmitted agents, reduced susceptibility to reinfection is particularly important since it operates to inhibit spread of such agents in the population. As the number of susceptibles in the population is reduced, there is a corresponding reduction in the likelihood that an infected individual will make effective contact with a susceptible. While other factors such as social behavior, frequency of contact, and physical environment (e.g., temperature, humidity) affect infectivity, the net inhibition of spread reduces the risk of infection for the remaining nonimmune members of the population. This phenomenon of "herd immunity" and its application to immunization strategies will be considered in a later section.

In general, protective immunity to infection depends on humoral antibodies. However, the relatively normal clinical response of persons with agammaglobulinemia to most viral infections suggests that other forms of immunity such as cell-mediated immunity may play important protective roles in the natural course of viral infections. Conversely, delayed hypersensitivity mediated by cellular immunity may also be a major determinant in the clincial symptoms of viral infections, e.g., the rash of measles.

Protective antibodies are specific for surface antigens of viruses. These antibodies can be induced by the whole virus (during infection or as incorporated in an inactivated vaccine) or by purified viral surface antigens. The protective effect of an antibody depends on its reaction with extracellular virus to form complexes which lead to noninfectivity.

Intracelluar virus is not affected by antibody. Thus, once infection has been initiated, the role of an antibody is limited to restricting the spread of virus. Since effective levels of serum antibody rarely develop in response to infection until most, if not all, susceptible cells have been infected, antibody is not thought to play an important role in recovery from viral infections. Thus postexposure use of immune serum globulin containing specific antiviral antibodies is protective only within a limited period after exposure. In addition, use of vaccines to stimulate active immunity is usually protective only when vaccination is begun substantially before exposure occurs (rabies constitutes a possible exception).

The protective effect of humoral immunity, including that induced by vaccines, depends on several factors. One is the relation between antibody titer and the exposure dose of virus. Under naturally occurring conditions, variation in infecting virus dose is probably fairly narrow, thus antibody titer is the usual determinant of whether infection will take place. Even when infection does occur, the antibody tends to restrict spreading of the virus, thereby minimizing the resulting disease. This is a beneficial effect of vaccine-induced immunity that sometimes is overlooked.

While the general rule is that antibody is most protective against the homologous agent, the immunity related to it will be protective against heterologous but related agents to a degree corresponding to the strength of the antigenic cross-relation between the agents. Such heterologous immunity is a potentially important determinant of the natural occurrence of infection and disease and may be an important consequence of vaccine-induced immunity, most notably in the case of vaccinia and smallpox.

Perhaps the most important area relating to the protective effect of humoral antibody is the pathogenesis of infection and disease. Since our concern here is entirely with the acute events following infection from exogenous sources, the development of persisting infection (latent, recrudescent, or continuing patent) will not be discussed except as it relates to new exposures. Portal of entry, site of primary virus localization, target tissues or organs (disease sites), paths by which virus reaches such targets, and total viral replication are more easily illustrated by specific disease examples.

Yellow fever illustrates the situation in which the agent is introduced through

the skin and gains entrance rather rapidly into the blood stream resulting in wide dissemination throughout the host. The systemic nature of the infection permits extensive viral replication. A correspondingly large mass of viral antigen which stimulates a major antibody response may account for the usual lifelong persistence of antibody. The usual portal of entry through the skin exposes the infecting dose of virus directly to humoral antibody present in tissue fluids and blood so that full protection is usually afforded by any detectable level of serum antibody. This situation also exists for other viral and rickettsial agents transmitted by blood-sucking arthropods.

Measles represents a similarly systemic infection which differs chiefly in usual portal of entry, i.e., through respiratory and/or conjunctival mucous membranes. Presumably, the virus replicates initially in mucosal cells and then quickly gains entrance into the lymphatics and/or blood stream by which systemic dissemination occurs. The resulting immunity is effective and usually lifeling. While antibody of the IgA class, when present in mucous secretions, may protect the mucosal cells from infection, clinical disease depends on systemic spread. Because systemic spread generally would be prevented by even low levels of serum antibody, resistance to disease will be lifelong although reinfection may occur. Rubella, chickenpox, and, perhaps, mumps are other important examples of this class of diseases although exhibiting some differences.

The pathogenesis of poliovirus infections is somewhat more complex. The virus usually gains entry via the oropharynx and/or the lower alimentary tract and is shed more copiously from the latter for periods which may exceed 100 days. The virus penetrates the mucosa and localizes initially in the underlying lymphoid tissues (e.g., tonsils and Peyer's patches). Further spread may be by one or both of two paths. Systemic dissemination via the blood probably occurs in all cases and helps insure the abundant antigenic stimulus which results in long-lasting seroimmunity. The motor neurons of the spinal cord and brain stem are the crucial sites of the only significant disease process (that causing paralysis). Fortunately, such central nervous system (CNS) involvement is very rare (1 in 200 to 800 infections). The ususal protective effect of passively transferred serum antibody (demonstrated experimentally in monkeys) suggests that CNS invasion usually is via the blood stream. However, autonomic and olfactory nerve fibers constitute a proven (again in monkeys) alternate path, which would explain the ready induction of paralytic disease following enteric infection in monkeys possessing high titer, homotypic serum neutralizing antibody induced by nonreplicating (Salk-type) vaccine, and also explain the surprisingly large number of cases of paralytic disease in persons with a history of three or more inoculations of Salk vaccine. Natural alimentary tract infection results in substantial but relative resistance to reinfection which depends on antibody of the IgA type present in mucous secretions. Such antibody is induced by inactive poliovaccines only when the vaccines are highly potent. In summary, serum antibody appears to be highly effective in preventing CNS invasion by the blood stream route but affords negligible protection against lower alimentary tract infection. If this occurs, CNS invasion by the nerve fiber pathway remains possible, even though serum antibody is present and the infected host may be a significant source of infection to others.

Influenza viruses, Types A and B, represent agents which may invade the lower respiratory tract where ciliated mucosal cells are the primary sites of localization. Disease results from the destruction of cells lining the tracheobronchial tree and the spread of virus to bronchiolar cells and cells of the alveolar septa. Although viremia is not a prominent feature of infection, viral relication in the nonimmune host is extensive enough to induce major antibody response. However, the effectiveness and durability of postinfection immunity are highly dependent on the degree of antigenic shift by subsequently infecting viruses. Protection of the mucosal cells from infection depends largely on secretory (IgA) antibody. Antibody in serum and tissue fluids (IgA) is believed important in limiting spread of virus from these superficial, primarily infected cells and, as a result, may afford significant protection against disease.

Noninfective Vaccines and Live Viruses

A reasonable goal of vaccine-induced immunoprophylaxis is to achieve a durable, protective immunity against both infection and disease comparable to that which follows natural infection, but with a greatly reduced or negligible risk of disease. Viral vaccines fall into one of two basic types, viz. those which contain nonreplicating antigens and those which contain a viable agent and so immunize by infection. This section will consider the known and potential advantages and disadvantages of each type.

1. *Noninfective vaccines.*—a. *Potency and effectiveness.* To be effective, an immunization schedule using noninfective vaccines must provide an antigenic mass sufficient to elicit an immune response of adequately protective and durable degree. Thus, vaccine potency is the most important criterion for effectiveness. Therefore, the dosage should be established in appropriate clinical trials with selected nonimmune volunteers.

The ultimate measure of vaccine effectiveness is protection against infection and/or disease. This ordinarily is demonstrated directly in small-scale, well-controlled experimental challenge studies and/or in carefully designed field studies during outbreaks which provide a natural challenge. From such studies, or from observations of the effectiveness of naturally-acquired immunity, it is usually possible to determine the type and the relative titer of serum antibody that correlates with protection. If this has been established for a specific agent, the antibody response of vaccinees may afford an acceptable basis for evaluating vaccine effectiveness.

The immunogenicity in man of particular lots of vaccine should be predictable from in vitro assays of specific antigen content and/or from tests for immunogenicity in experimental animals. Immunogenicity for man will, of course, also depend on the size, number, and spacing of vaccine doses (a single dose is the ideal). The need for multiple doses is an obvious public health disadvantage, which possibly might be overcome with the use of adjuvants.

The noninfective vaccines currently licensed are administered parenterally, either subcutaneously or intramuscularly. Possibly because this results in little or no stimulation of secretory antibody, such vaccines afford only relative protection, or no protection, against infection via mucosal portals of entry. Hence, the vaccinee may be protected against disease, but once infected he constitutes a potential source of infection for susceptible contacts. This possibility is lessened if the immunity engendered reduces the amount and/or duration of virus excretion.

The durability of immunity induced by noninfective vaccines can be established by monitoring serum antibody levels in individuals who are not exposed to infection. Generally, in the absence of natural restimulation, such immunity will wane. However, after primary immunization, the host is

specifically conditioned to respond quickly and in high degree to new stimulation. Depending on the length of the incubation period of the disease, this enhanced responsiveness may be sufficiently rapid, when triggered by natural infection, to protect the host against disease.

b. *Possible adverse effects.* These relate to the viral antigen and to the menstrum in which it is contained.

(1) *Viral antigen.* first, there may have been failure to fully inactivate the virus, so that infection and disease may occur, e.g., the so called Cutter episode with Salk poliomyelitis vaccine. (For a discussion of the Cutter episode see Ref. 1) Second, the inactivated antigen may be toxic and cause local and/or systemic reactions, e.g., influenza vaccines. Third, the vaccine may induce hypersensitivity to the viral antigen without inducing protection against infection. As a result, the vaccinee may become susceptible to disease of unusual severity from natural infection with wild-type virus, such as has occurred following immunization with inactivated measles virus vaccine.

(2) *Vaccine menstruum.* Virus for noninfective vaccines is usually propagated in nonhuman cells. The final preparation of viral antigen (vaccine), therefore, may contain host tissue components, trace amounts of antibiotics, small amounts of formalin (or other chemicals) used to inactivate the viral antigen(s), viral components, and killed bacterial contaminants such as endotoxins, etc. although infrequent, sensitization to the host tissue can result in significant disease if the sensitization is organ specific (e.g., sensitization to CNS constituents induced by rabies vaccine). While, in theory, repeated use of a vaccine might induce sensitivity to other nonviral components, the greater hazard relates to reactions elicited in vaccine recipients already sensitive to one or another such component (e.g., antibiotics, traces of substrate, or even formalin). Residual formalin usually causes only slight, transient pain at the site of inoculation. ordinarily, formalin, or other chemical agents will also inactivate microbial contaminants, but this inactivation may not be complete (e.g., SV–40 virus in earlylots of inactivated poliomyelitis vaccine). Bacterial endotoxins pose a particular problem for vaccines produced from egg-grown viruses (e.g., influenza virus) because of the apparent difficulty in avoiding contamination with gram-negative bacteria. If present in sufficient quantity, such endotoxins may cause significant, acute systemic reactions. Menstruum problems concern both noninfective and live virus vaccines, but generally are under better control in the latter.

Although generally considered safer than live virus vaccines, noninfective vaccines are characterized by multiple-dose inoculation schedules, protection against disease but not necessarily infection, relatively short-lived immunity, and an increased likelihood of adverse reactions associated with their administration.

2. *Live virus vaccines.* The basic idea of live virus vaccines is simple but the relevant considerations are numerous and complex. A strain of the virus (or of an antigenically similar agent) must be found or produced, which will induce in man an immunizing infection with an acceptable or negligible risk of disease. Relevant considerations include finding or producing a suitable genetically stable strain of the virus, recognizing its avirulent character, determining the minimal consistently infective dose, demonstrating the effectiveness and durability of the resulting immunity, and establishing both primary safety (for the vaccinee) and secondary safety (for the vaccinee's contacts). These points are considered very briefly in the following presentation along with an abbreviated discussion of issues concerning substrates used for vaccine production.

a. *Origin of candidate attenuated virus strains.* The ability to test candidate strains for possible avirulence requires a suitable animal model (e.g., the monkey for yellow fever virus or poliovirus) or the possibility of using human volunteers (for agents causing disease with minimal risk of serious sequelae). Viruses undergo spontaneous mutation at rates dependent on many factors. The mutations result in virus populations that are heterogeneous with respect to various characteristics including the ability to infect and to cause disease in man. Historically, a variety of approaches have been employed to segregate avirulent strains from viral populations containing wild-type characters. These approaches include the use of isolates from naturally occurring subclinical infections, passage in unnatural animal hosts or in tissue culture systems held at low temperature to provide an environment favoring replication of the avirulent particles or cloning parental populations. Ultimately, it is desirable when possible to produce clones (strains deriving from single virions) which are genetically homogenous (at least originally) and genetically stable, and can be tested for their ability to infect and cause disease.

Testing for avirulence is a major problem in the assessment of live virus vaccines. It is made easier if an appropriate animal model for the disease exists (e.g., the rhesus monkey for yellow fever, poliomyelitis, and measles). Nevertheless, in all instances final testing for avirulence must be conducted with human volunteers. If no animal model exists, the initial testing must be conducted with humans.

Once an acceptable avirulent strain of virus (candidate vaccine strain) is found, the inherent mutability of viruses makes testing the genetic stability of the strain with respect to virulence properties as it is propagated for production of vaccine lots and as it replicates in vaccinees imperative. While further direct testing of ability to cause disease may be necessary, on occasion, this may prove cumbersome and, if human volunteers are necessary, almost prohibitive. This makes comparative studies of avirulent and of wild-type virus strains highly desirable to determine those in vitro characteristics which correlate with virulence or avirulence. When genetic markers which differentiate avirulent from wild-type strains have been identified, examination of new vaccine lots and of viral isolates from vaccinees for these markers may serve as a monitor on the overall genetic stability of the vaccine virus strain. Such monitoring is based on the assumption (not fully justified) that if these markers maintain their character, the avirulence character probably is also unchanged. Changes occurring during replication in the vaccinee are of concern chiefly if spread of the virus to susceptible contacts is possible. Changes which occur as new vaccine lots are produced pose a potential hazard to the vaccinees themselves. The likelihood that genetic reversion will occur can be minimized by use of the "seed lot" system in producing vaccines so that no production lot represents more than three to five passages from an original, thoroughly tested "master seed" (see Recommendations).

b. *Potency and effectiveness.* Since live virus vaccines immunize by inducing infection in the recipient, establishing the minimum dose of vaccine virus required to infect the nonimmune recipient is essential. When this is known, the potency of the vaccine is evaluated simply on the basis of an in vitro assay of its infective titer.

Considerations relating to vaccine effectiveness are essentially similar to those outlined with respect to noninfective vaccine. Maternally derived antibody persisting during the early months of life, may establish an age limit below which vaccination,

particularly by parenteral routes (e.g., measles and rubella) may be less effective at reasonable virus dosage levels. Another important factor is "interference" by which a concurrent infection with a wild virus, or with another vaccine virus, blocks infection with the vaccine virus administered. This has been observed with orally administered poliovirus vaccine and may prove important for possible live respiratory virus vaccines (e.g., influenza).

Experience with current live virus vaccines indicates that excellent and durable immunity against both disease and reinfection can be induced by a candidate vaccine which meets the conditions discussed above. Thus, recipients of a live virus vaccine are effectively removed from the pool of susceptible individuals and ordinarily will play no future role in the spread of the virus within the population.

c. *Consideration of safety.* As discussed in the context of the noninfective vaccines, live virus vaccines contain host cell components, a dose of viable attenuated infective virus, and often a stabilizer. With the exception of smallpox vaccine (vaccinia virus), current live virus vaccines contain very low amounts of host cell proteins. They are presumed, on the basis of current technology, not to contain any known viruses other than the vaccine strain itself (yellow fever vaccine is an exception, and this situation is now being corrected).

(1) *Substrate.* One present concern is with viral contaminants. These may be introduced during the production process or, more likely, may have been present in the cell substrate. This latter possibility is closely related to the origin of such cells and can be reduced (or virtually eliminated) by use of established cell strains (e.g., WI–38 diploid cells of human fetal origin). The established cell strains must be studied for the presence of extraneous agents or must be obtained from cells from animal or egg that are specific pathogen-free. Reliable detection of known viruses is technically possible, although the procedures presently prescribed need to be improved. Since, with the exception of B virus (*Herpesvirus simiae*) from monkeys, the pathogenic potential for man of the recognized indigenous viruses is either not known or believed to be negligible, failure to detect their presence is of unknown importance.

The presence of host cell genetic material and the possible presence of unknown, potentially oncogenic viruses in live virus vaccines poses theoretical risks to vaccine recipients. These risks are best managed by careful monitoring of both the vaccine and its recipients. (However, the problem posed may be more difficult than a quick appraisal suggests. Recognition that a vaccine contains a heretofore unknown viral contaminant of undetermined pathogenicity for man is an epidemiologic problem which will be discussed in a later section.)

Since viruses grow inside cells, the final licensed product actually represents the net product of a particular virus-cell interaction. One poorly understood aspect of this interaction is the influence of the cell on the virulence of the vaccine strains of certain viruses (e.g., poliovirus and rubella). The inability to predict the effect of a particular cell on a given virus property such as reversion rate to neurovirulence (poliovirus) or a side effect such as arthritis (rubella) emphasizes the need for careful clinical trials prior to licensing. Perhaps equally important is the need to support more research into the mechanisms which lead to a loss of undesirable viral properties and to the acquisition of beneficial properties.

(2) *Vaccine virus.* Infection with an attenuated virus may give rise to an attendant immediate effect or to a long-delayed adverse effect. The first concern is with the immediate adverse effects. The frequency and severity of adverse effects in vaccinees are important criteria in determining vaccine acceptability. Also, in view of the immediacy of these reactions their evaluation should be quick and straightforward by means of simply designed clinical trials. The difficulty with such trials lies in size rather than design. To provide assurance that a truly serious outcome will occur in no more than 1 in 10,000 vaccinees would require observation of 100,000 or more individuals. It should also be remembered that the outcome of infection is partly determined by host factors, age in particular. In the nonimmune host, the consequences of infection usually are potentially most important in infancy, least in early childhood, and increasingly important with advancing age thereafter. Thus, if contemplated use of the vaccine includes adults, this age group should be included in the clinical trials. The possible important of pregnancy usually must be deduced from observations on naturally infected pregnant women (and their fetuses). Primary immunologic deficiencies and diseases or therapeutic measures known to impair the normal immune response also are of concern. Once again, evaluation of the part played by immunologic defects hinges on the experience of such deficient patients undergoing a natural infection, or responding to vaccine administered inadvertently.

Shedding by a vaccine recipient of sufficient virus to infect susceptible contacts raises concerns about their risk. As noted previously, an attenuated vaccine virus replicating in the human host may undergo reversion towards the wild type acquiring virulence characteristics. Hence, clinical trials should include studies of two types: (i) analysis of situations (classrooms and/or family units) in which spread to susceptible contacts can be observed and outcome of contact infections evaluated, and (ii) characterization of viral isolates collected from the vaccinees and from infected contacts for evidence of reversion. If contact spread appears to pose a hazard, this should be taken into account in recommendations of vaccine use.

The long delayed adverse effect of a live virus vaccine would depend on a persistent but possibly latent infection. Thus far, no current vaccine virus strain and, with the exception of measles and perhaps rubella, no corresponding wild-type virus has demonstrated such effects. Subacute sclerosing panencephalitis (SSPE), a presumed late and rare consequence of natural measles, is a theoretically possible effect of measles vaccine. (See Generic Reivew of Measles Virus Vaccine and discussion of safety under the summary of this section.)

In summary, live virus vaccines overcome most of the objections raised concerning noninfective vaccines in terms of ease of administration, protection, and durability of protection. However, live virus vaccines are very complex materials genetically and their safe use in man requires careful controls and extensive experience. Under proper conditions, live virus vaccines are safe and effective.

Summary—Live Virus Versus Noninfective Vaccines

1. *Administrative considerations.*—a. *Live virus vaccines.* A single dose ostensibly suffices for parenterally administered vaccine. Except for vaccinia and influenza virus vaccines (when such become available), the need for reimmunization is questionable and probably is required only after a long interval. For orally administered poliovirus vaccine, multiple feedings are recommended to ensure that gastrointestinal infection is established.

b. *Noninfective vaccines.* Primary immunization generally requires a course of two or more doses and maintenance of immunity usually

requires periodic enhancing (booster) innoculations.

2. *Effectiveness and duration of immunity.*—a. *Live virus vaccines.* (1) Measles and yellow fever vaccines give long-lasting (10 or more years) solid immunity against disease and relative protection against subclinical infection.

(2) Oral poliovirus vaccine provides a long-lasting highly effective protection against disease and relative high protection against infection.

(3) Smallpox vaccine provide highly effective protection for a limited period (1 to 3 years).

(4) Rubella and mumps vaccines provide effective protection against disease but the duration of protection has not been established.

b. *Noninfective vaccines.* (1) Inactivated poliomyelitis vaccine is about 95 percent effective against paralytic disease based on experience in the United States, but is relatively ineffective against enteric infection. The duration of immunity is not firmly established. (However, the Swedish vaccine, which seems to be more potent than the early United States vaccine, is apparently effective against infection as well as disease.)

(2) Influenza vaccine is relatively (70 to 80 percent) effective against disease caused by the homologous virus and less effective against subclinical infection. The duration of protection is limited inpart by continuous changes or shifts in the antigenic character of the wild virus.

(3) Rabies vaccine represents a special case. Except in the case of high risk populations (for instance veterinarians) the vaccine is seldom given in the absence of-prior exposure.

3. *Safety.*—a. *Live virus vaccines.* Some licensed vaccines cause minor systemic reactions in 5 percent or more of recipients. Vaccinia virus causes true although usually mild disease in 100 percent of successful vaccinations. Serious reactions which are not always clearly caused by the vaccine have been observed in recipients of all live virus vaccines and are extremely infrequent. The best verified instances (and of greatest concern) are those which may follow smallpox and live poliovirus vaccines. Spread of the virus to contacts with subsequent induction of disease has been verified only for polio and vaccinia viruses. Only in the case of early lots of yellow fever vaccine (which contained human serum as a stabilizer) has disease (hepatitis B) caused by a viral contaminant been recognized.

b. *Noninfective vaccines.* The presence of residual live virus has posed a problem only with poliomyelitis vaccine (the Cutter episode; also the presence of SV–40 virus in many lots of vaccine produced between 1955 and 1960). Local and, especially in children, systemic reactions have followed influenza vaccines and have been attributed in part to a toxic effect of the viral antigen. Isolated instances of allergic reactions have been reported in individuals sensitive to egg proteins who received vaccines (influenza and typhus) prepared for egg-grown agents. Vaccine failures, marked by naturally contracted disease, are relatively common despite "adequate" immunization and warrant consideration in relation to vaccine safety.

4. *Contribution to herd immunity.*—a. *Live virus vaccines* make a substantial contribution to herd immunity since successfully vaccinated persons play no future role in spread of the agent.

b. *Noninfective vaccines* make a doubtful or unclearly established contribution. In addition, vaccinees commonly acquire natural infection and often shed enough virus to permit spread to contacts.

The Problem of Subtle and/or Long-Delayed Adverse Effects of Vaccines

In the previous section which considered the adverse effects and safety of vaccines, the possible long-delayed effects were only briefly mentioned. The precise nature of such long-delayed effects is not pertinent to this discussion unless they are identifiable and significant. Indeed, one should be prepared for effects of a completely unforeseen nature. The problem is how to recognize that a relation may exist between administration of a vaccine and instances, perhaps rather isolated, of disease occurring in persons who had received the vaccine at variable but lengthy intervals before the onset of the disease. The value of animal models in the solution of this problem is clearly limited. This problem cannot be solved completely in the abstract and may never be solved in specific instances. Nonetheless, awareness of its existence is important, and approaches to its solution should be developed. It is also important to note that this problem is related to theoretical consequences of vaccination. These consequences are sufficiently tenuous in prospect that when the public health benefits of a given vaccine are under assessment, the risks should not be given undue weight in estimating the benefit/risk ratio of that vaccine.

A basic proposition in epidemiology is that associations consistent with a causal relation are not discovered until the possibility that they exist is recognized. Historically, epidemiologists start with a defined disease and search for its causes. Typically they begin with a case-control (retrospective) study in which "possibly significant experiences" of cases are compared with those of appropriate controls. The decision as to what constitutes "possibly significant experiences" is crucial. The recent "epidemic" of clear-cell adenocarcinomas of the vagina and cervix in adolescent and young adult females is instructive. Someone, either fortuituously or possessing unusual insight, decided to explore the antenatal as well as the postnatal experiences of the patients and the controls. As a result, it was found that diethyl stilbesterol (DES) given to the patients' mothers to counteract threatened abortion was clearly incriminated. The important point is that in future case-control studies of diseases of uncertain etiology, a history of prior immunization (both antenatal and postnatal) must be included in the list of "possibly significant experience."

An opposite but highly relevant approach begins by regarding vaccines as possible causes of diseases yet to be specified. This dictates that vaccine recipients (and some appropriate control group) must be followed indefinitely for the occurrence of significant illnesses. The practical problems of this approach are obvious and, at first glance, so overwhelming that one is tempted to abandon it forthwith. Which recipients? Who would be appropriate controls? How large should the comparison groups be? By what mehcanism and by whom would the follow-up be implemented? Before taking up these questions, we should consider possible patterns of occurrence of vaccine-induced disease and existing or potentially retrievable information on vaccine usage and possibly related disease.

Except for smallpox vaccine, viral and rickettsial vaccines are relatively recent developments, appearing since the late 1930's when yellow fever vaccine was introduced. Since then, new vaccines have been introduced and substantial information exists concerning how much and in what target populations they have been used. Also, much information exists in more or less readily available records concerning both significant morbidity and mortality in the United States population. Finally, large numbers of persons who were vaccinated, and those who were eligible but were not vaccinated, still survived. Conceivably, such survivors can be identified and investigated for disease experience that may have escaped

recording and can be followed for future disease experience. In summary, a large mass of information exists which, although difficult to explore, could greatly hasten recognition of significant, long-delayed adverse effects of specific vaccines.

Assuming that a given vaccine does cause delayed effects, what are possible distinctive features of the vaccine-disease relation? First, a temporal clustering of cases reflecting the incubation period should be evident when disease onsets are plotted on a time axis which begins with date of vaccination. The demonstration of such clustering constitutes a forceful argument for etiologic relationship in the absence of case-control comparison. Related to this, a time plot of numbers of persons vaccinated should rise in parallel with later increasing incidence of the related disease. Next, occurrence of disease may be strongly influenced by one or more host characteristics of which age and perhaps sex are most likely to be important. By analogy with observations in laboratory animals, infants and very young children should be most vulnerable to any oncogenic effects of a vaccine-transmitted virus. Realization that such host factors may operate is clearly important in exploration of the relation between vaccination and vaccine-induced disease.

The Panel's concern and that of FDA, is with determination and establishment of the standards for acceptable safety of vaccines. Hence, beyond trying to educate epidemiologists to include evaluation of immunization histories in case-control studies of disease etiology, a basic approach assumes that vaccines may cause diseases of unforeseen nature after long, but temporarily unknown, incubation periods. The only possible design is a cohort (or prospective) study in which vaccine recipients and comparable controls are monitored over an extended (perhaps indefinite) period. Ideally, provision for such a study should be made in planning and conducting the clinical trials that are required to establish vaccine safety. Volunteers would first be screened to identify susceptibles. Under current practice, the susceptibles are formed into two groups, one to receive vaccine and the other a placebo. For obvious ethical reasons, if the vaccine proves both effective and of acceptable safety, the placebo group must subsequently also be offered the vaccine and, hence can no longer serve or be useful as a long-term control. The revised design would then utilize the volunteers found to have been naturally immune as a third comparison group for prolonged observation. Vaccinated members of the original placebo group would be combined with the original vaccine group for extended observation. If the comparison groups are large enough, such a design would permit detection of the effects of a possible viral contaminant, and also of possible undesirable properties of the vaccine virus acquired through genetic reversion or mutation during propagation in cell cultures.

The necessary size of the comparison groups depends on the estimated rate of loss to followup and how one defines acceptable safety. Presently, acceptance of a new live vaccine virus strain requires that it cause no significant acute disease in a specified large number of susceptible vaccines. Observation of 10,000 vaccine recipients would afford reasonable assurance that, in normal use, no more than one individual in 1,000 would experience a significant serious consequence. The study design suggested above would provide an initial vaccine group of about twice that number but the size of the long-term comparison group would depend on the extent of prevalence of natural immunity. Current regulations for some of the viral vaccines such as rubella require that the manufacturer obtain (and transit to the Bureau of Biologics) identifying information sufficient to permit a followup of 5,000 vaccinees. This design would require such information for all members of the two long-term comparison groups. Since the adequacy of the control group suggested here is open to question with respect to size, and to a possible confounding effect of natural acquisition of immunity in this group (natural infection in some members may give rise to delayed consequences similar to those referable to the vaccine virus strain), it should be recalled that analysis of the experience of the vaccine recipients alone should be revealing, i.e., vaccine-related disease should show clustering in time and the frequency might vary with age and sex. The followup operation is clearly feasible, although admittedly costly. Who should be responsible for it is a political question, but simple logic would suggest FDA or the Center for Disease Control (CDC), both part of the Public Health Service (PHS).

How the foregoing design can be applied to vaccines already licensed is more difficult to determine. One highly unacceptable possibility is to conduct new trials for long-term followup only. More realistically, attempts should be made to identify those persons who received a specific vaccine soon after it was introduced.

For vaccines licensed in recent years, such approaches would include thousands of participants in the original clinical trial who were identified by the manufacturer. Others might be identified from the records of health agency immunization clinics, prepaid medical care plans, etc. Construction of truly appropriate control groups poses such a seemingly insoluble problem that evaluation of the vaccines might have to rest entirely on the experience of the vaccinated individuals. However, at least some control groups are possible. For the reportable diseases, persons who experienced the disease (and presumably had not been vaccinated) might be identified. Aslo, for vaccines used largely during childhood, individuals whose childhood shortly preceded the advent of the vaccine could be identified. Finally, the experience of persons identified as recipients of one vaccine could be compared with that of recipients of other vaccines. Undoubtedly, other possibilities exist, but the main point is that it should be possible, with respect to current vacines, to take advantage of the experience that has accumulated since the vaccines were licensed and thereby hasten the recognition of their possible adverse effects.

Problems Involving Political and Ethical Considerations

The approval and licensure of vaccines, the development of standards for effectiveness and safety, and policies concerning recommended usage of vaccines involve judgments and decisions which are based only in part on scientific knowledge. The following is an examination of some of these problems together with a few notes intended to identify the nature of the pertinent considerations. In none of these problems is vaccine effectiveness the issue, although the degree of effectiveness may be a factor.

1. *The clinical trial to explore safety.* Scientifically, using the established design of double-blind studies with placebo controls, a clinical trial can yield reliable estimates of the risk of serious consequences, of whatever degree, associated with a vaccine. For estimation of very small risks, larger numbers of volunteers are required. The questions at issue are: "What degree of risk is acceptable?" and "How does one define serious consequences?" The answers are obviously influenced by any sequelae associated with the naturally occurring disease and with the risk associated with other available preventive measures. These are value

judgments and cannot (or should not) be made only by scientists. The more difficult question concerns the acceptable degree of risk. The answer to this question determines the required size of the clinical trial.

It was emphasized earlier that host factors, age in particular, may play an important part in response to viral infection. This is particularly relevant to live virus vaccines. Hence, the clinical trial should include individuals of all age groups likely to receive the vaccine. For most vaccines, infants and young children comprise the primary target population. The ethical problem of gaining fully informed consent for such young individuals is well recognized but is emphasized here as a clearly restrictive factor which affects the conduct of adequate trials. An obviously helpful aspect is that, in most cases, the young volunteers would benefit from the immunization.

2. *Benefit/risk ratio.* The ultimate approval of a vaccine hinges heavily on the benefit/risk ratio. This term implies a quantitative formula which, unfortunately, is not attainable with exactitude. However, as a statement, it does carry the important implication that measurable risk is not of itself an adequate reason for disapproval, a decision to be made only after assessment of possible offsetting benefits.

Both benefit and risk can be expressed as quantitative estimates which, however, often are not fully reliable. These can be expressed in terms of individual risk, e.g., vaccination is associated with a possibility of one per million that serious related disease will occur as compared with a lifetime risk of one per thousand that serious natural disease will occur if no vaccine is given. According to these estimates, the odds that an individual will not experience specific serious disease are improved 1,000-fold by vaccination. The problem also can be viewed in terms of an entire population. Using the probabilities suggested above, vaccination of a million young children would eventuate in one case of serious disease whereas without vaccination some 1,000 individuals in this age group would eventually acquire such disease during their lifetime. With the comparative risks as stated, approval would be clearly indicated.

Unfortunately, the problem is seldom so clearly delineated. Often, alternative effective methods of prophylaxis may already be available, e.g., noninfective versus live virus poliomyelitis vaccine. This particular example serves to illustrate a number of other factors that must enter into any assessment. One factor is vaccine cost. The viral antigen content of inactivated poliomyelitis vaccine must be much greater than that of a live virus vaccine, and hence its cost presumably is greater. Another is acceptability; live virus vaccine, because it is taken by mouth rather than via a needle, is much more acceptable, a factor important to extending immunization to the lower socioeconomic segments of the population. Still another factor is the possible benefit to susceptible members of the population who may escape vaccination. Because the killed-virus poliomyelitis vaccine affords little protection against intestinal infection, recipients may continue to participate in the spread of wild poliovirus whereas recipients of live virus vaccine become highly resistant to infection and usually play no further role in viral spread. Thus, extensive use of live virus vaccine reduces the probabilities that unvaccinated susceptibles will be infected with wild virus.

In the above discussion, "serious consequences" were not defined. If these include possible lethal outcome, they take on additional weight and especially so in the case of a vaccine used against a rarely lethal disease. This latter situation has not yet been encountered. However, in this connection, concerns have been expressed about potential oncogenic effects due to presence in the vaccine of unknown viral contaminants, or to genetic fragments of oncogenic viruses somehow incorporated into the genome of the vaccine virus. As suggested previously, such a theoretical risk should carry little or no weight in estimating the benefit-risk ratio when, on practical grounds, the ratio is highly favorable. Nevertheless, even the theoretical possibility of such risk makes it mandatory to maintain a continuing surveillance to detect the postulated effects and to reevaluate the benefits against the risk if such effects are recognized.

Another major consideration is economic, which for lack of adequate data often is ignored. These data would contrast the cost of a vaccine and its administration plus the costs (medical care, rehabilitation, impairment of ability to earn income) of vaccine-related disease with costs of a similar nature that would have accrued from cases of the natural disease. For an "acceptably safe" and effective vaccine against a serious disease, again the ratio should be highly favorable. However, if the preventable disease occurs chiefly in young children and is infrequently associated with permanent sequelae, a different answer might result. The question then might become "how much cost can be justified to prevent one crippling or lethal case of disease?" This clearly requires a societal rather than a scientific judgment.

3. *Recommendations for vaccine usage.* Vaccines necessarily are administered to individuals under the direction of a physician as part of a program for protection of the recipient as an individual, or as part of a publicly sponsored or encouraged program directed toward control of the specific disease. In their use of vaccines, physicians are guided by "official" recommendations which typically indicate who should be immunized, the circumstances requiring or justifying immunization, any specific precautions that should be observed, and absolute or relative contraindications to vaccination. Inattention to precautions and contraindications may constitute medical malpractice although the decision to vaccinate is otherwise basically left to the physicians' judgment.

While vaccination must afford benefit to the recipient, it is also usually a matter of public concern. At the least, the illness prevented obviates loss of time from school or work and lessens by one case the need for medical services and facilities. For vaccines which protect effectively against infection as well as disease, extensive vaccination makes contact spread more difficult. Thus, the risk of disease is reduced for any remaining unvaccinated susceptibles. If the vaccination program is sufficiently extensive and sustained, eradication of the wild-type virus from increasingly large geographic areas may be an attainable goal.

The Federal government has accepted responsibility, implemented by the PHS Advisory Committee on Immunization Practices (ACIP), for the development and promulgation of recommendations on vaccine use. An additional advisory group, theoretically independent but in practice closely coordinated with ACIP, is the Committee on Infectious Diseases of the American Academy of Pediatrics whose parallel recommendations, largely focused on pediatric use of vaccines, appear in its periodic report (known as the "Red Book"). The published recommendations reflect public policy and serve as a guide to the use of vaccines in populations as well as in individual cases. Exampls are the efforts to increase the use of measles and poliomyelitis vaccines to achieve virtual eradication of the wild agents, and to concentrate on prepubertal children as recipients of rubella vaccine

to reduce the chance that susceptible women will be infected during pregnancy.

The FDA through the Bureau of Biologics is charged with approval and licensure of vaccines and regulation of their production, packaging, advertising, and release. The packaging aspect covers the inserts which contain recommendations on use, statements of risk, etc. Inevitably, decisions concerning approval also involve consideration of how a vaccine will be used. On this point, there is some overlap in attitude and philosophy with ACIP, but there is no question that the matters of safety and effectiveness are, by law, the responsibility of the Bureau of Biologics. Since both factors are potentially influenced by how the vaccines are used, the Bureau of Biologics also should be basically responsible for promulgating vaccine usage recommendations. In view of the present commendable collaboration between CDC (and its ACIP appendage) and the Bureau of Biologics, the question might appear to be academic, but it is nonetheless an important political question which should be further considered.

4. *Public liability for adverse effects of vaccines.* The intent of this section is to state briefly a very real problem which needs urgent resolution. Through FDA, the Federal government assumes responsibility for the effectiveness and safety of licensed vaccines. Through CDC, the government also has accepted responsibility for recommending how vaccines should be used. These responsibilities as noted above, reflect the major public interest served by vaccines; hence, the continued availability of vaccines is also a major public concern, and one which is now being threatened.

It is not possible to produce an effective vaccine that is absolutely and infallibly safe. Hence, an occasional recipient will suffer significant injury and, in at least some instances, unrelated disease when it coincides with vaccination will be (and has been) attributed to the vaccine. There is little argument but that persons truly injured by a vaccine should receive fair monetary compensation. However, under present circumstances they seek redress from the manufacturer and from the administering physician or nurse who have been held liable in the courts when adverse effects are judged due to a vaccine, even when it has been produced and administered in strict compliance with existing standards and regulations. The resulting judgments are causing such financial loss to the manufacturers that some at least are abandoning vaccine production, and others are said to be considering it. Indeed, for these reasons the continued availability of poliovirus vaccine is in serious jeopardy.

The obvious solution to this problem requires legislation. Victims of established adverse effects of vaccines which have been produced and released in full compliance with Federal regulations should be compensated adequately by the Federal government. Concomitantly, the manufacturer of the vaccine, assuming no culpability on its part, should be held free of liability. The laws enacted in Denmark and the Federal Republic of Germany provide for compensation from public funds to persons suffering damage consequent upon vaccinations that are recommended to the public by the competent authorities. In both countries, a reasonable probability of the causal relationship between the immunization and the injury is regarded as sufficient basis for payment of damages. In Germany, damages are paid as a pension, and this is the case also in Denmark provided that the disablement is 50 percent or more. If the disablement is less than 50 percent, damages are usually paid as a capital sum. Children, however, receive their compensation only after they have reached an age of 15 years. Below this age, financial aid can be obtained from public funds under the general social laws.

Reference

(1) Nathanson, N. and A. D. Langmuir, "The Cutter Incident," *American Journal of Hygiene*, 78:16–81, 1964.

Generic Review of Poliomyelitis Vaccine

Background

Poliomyelitis emerged in the late 1800's as a disease of significance in temperate zones. Its viral etiology was established in 1909 and the existence of three antigenically distinct serotypes was recognized in 1949. The work of Enders and his colleagues, beginning in 1949, demonstrated that polioviruses could be propagated in tissue and cell culture with easily discernible cytopathic effects. This landmark discovery opened the door to major studies which led to nearly complete epidemiologic understanding of the disease, basically because cell cultures replaced monkeys (1 tube culture = 1 monkey) for virus isolation attempts and for assay of neutralizing antibodies. More important, for present purposes, the discovery made possible the development and production of effective vaccines, first the inactivated virus type (inactivated poliomyelitis vaccine (IPV)) licensed in this country in 1955 and then the live attenuated virus vaccine for oral use (oral poliomyelitis vaccine (OPV)) licensed in 1961.

The situation in the United States immediately preceding and following the introduction of these vaccines for general use is summarized in Figures 1 and 2.

As shown in Figure 1, the reported incidence of poliomyelitis rose consistently from 1941 to an apparent peak in 1953 when nationwide attack rates reached nearly 23 per 100,000 for paralytic disease and 37 per 100,000 for all forms. The effectiveness of IPV is reflected in the dramatic decline in incidence of the disease after 1955. With the virtual replacement of IPV by OPV in 1962, incidence further decreased to the point where rates are no longer meaningful. The total number of paralytic cases in 1971, 1972, 1973, 1974, 1975, and 1976 was only 17, 29, 7, 4, 5, and 8, respectively.

The overall pattern of usage of vacines is reflected in Table 3 and Figure 2A.

The chief points of interest are: (1) from 1964 on, the distribution of IPV declined dramatically, reaching the point where it is now obtainable only with difficulty, although still licensed; (2) reflecting its use in large community-wide programs, monovalent OPV (MOPV) was most extensively distributed in 1962 to 1964; and (3) since 1966, trivalent OPV (TOPV) has virtually replaced MOPV. The reasons for these changes are fairly obvious. OPV is easier to administer than IPV is more acceptable, and the resulting immunity is more like that following natural infection, i.e., it is longer lasting and provides greater resistance to alimentary infection. MOPV represents three separate oral vaccines, thus making maintenance of stocks and keeping of records more difficult than with the single product represented by TOPV.

The most important remaining aspect of vaccine use is identification of the population segments which are not vaccinated. Even though OPV is readily more accepted than IPV, the problem remains a significant one.

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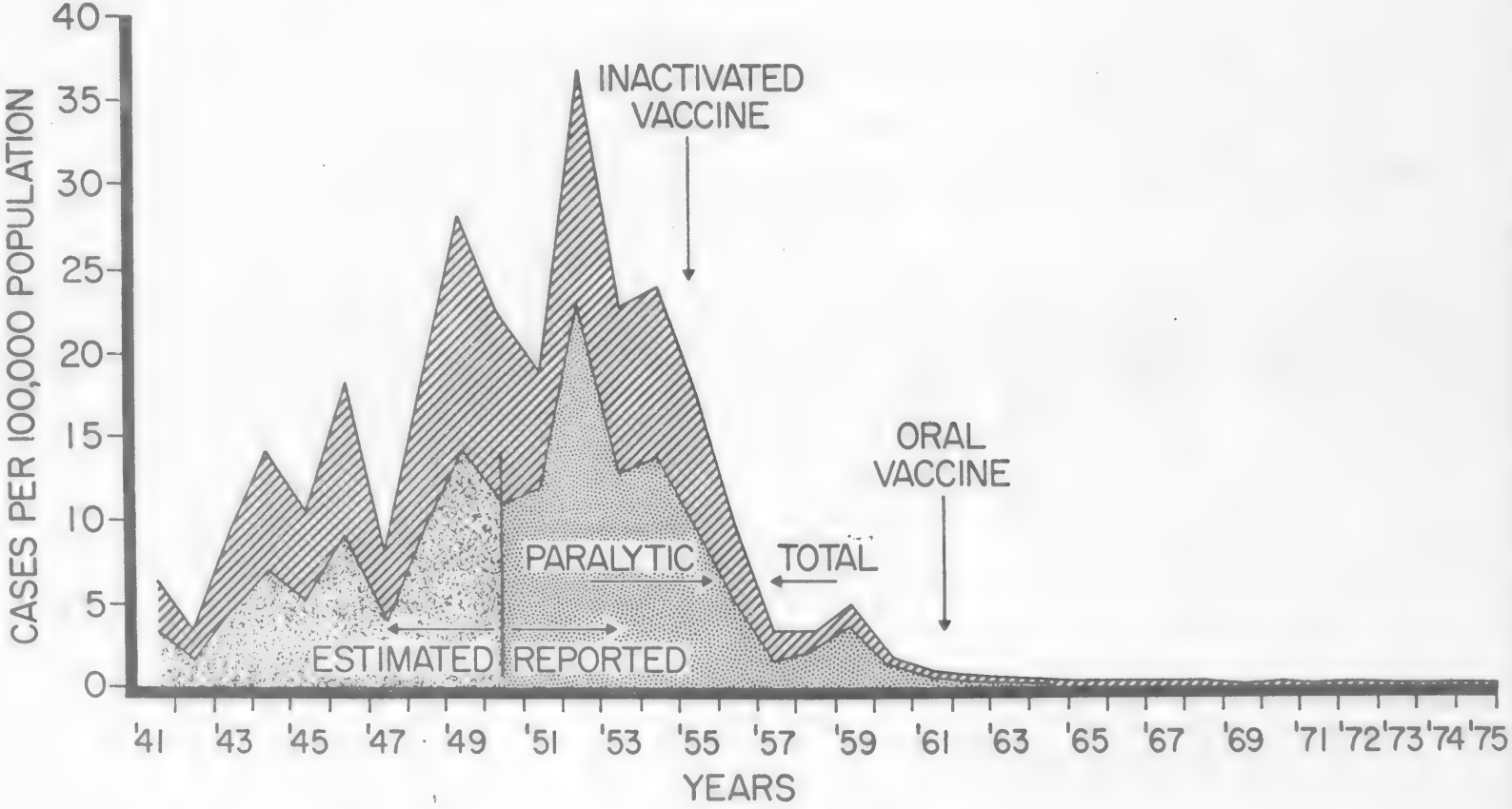
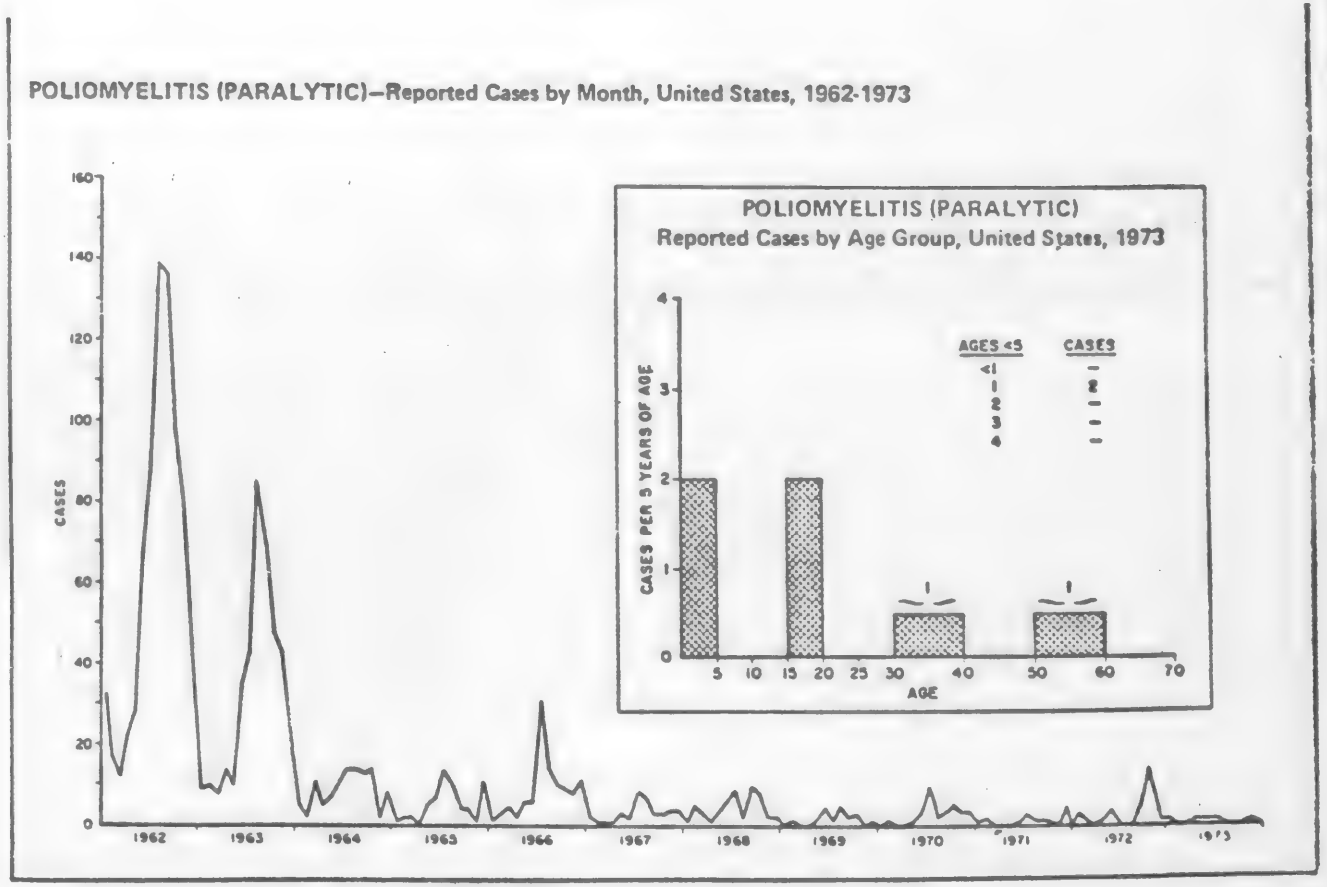
Figure 1

ANNUAL POLIOMYELITIS INCIDENCE RATES UNITED STATES, 1941-1975



Source: Center for Disease Control, Bureau of State Services, Immunization Division

FIGURE 2



SOURCE: Center for Disease Control, Bureau of Epidemiology.

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Table 3.—*Poliomyelitis Vaccine Distribution, Net Doses (Millions) by Year, United States, 1962–71*

	1962[1]	1963	1964	1965	1966	1967	1968	1969	1970	1971
Inactivated poliomyelitis vaccine (IPV)	15.3	19.0	8.8	7.5	5.5	4.0	2.7	[2]		
Oral poliomyelitis vaccine, live (OPV):										
Monovalent (MOPV):										
Type 1	33.1	38.7	24.9	4.7	1.4	1.3	0.5	0.4	0.3	0.2
Type 2	37.0	34.2	29.8	3.4	1.3	1.0	0.5	0.4	0.2	0.1
Type 3	13.7	54.2	28.4	3.7	1.4	1.0	0.5	0.4	0.3	0.2
Trivalent (TOPV)		[3]4.2	24.0	17.4	24.0	18.0	23.9	22.5	25.8	25.5
Total	99.1	150.3	115.9	36.7	37.6	25.2	28.2	23.7	26.6	25.9

[1] July-December (biologics surveillance program began July 1962).
[2] Not shown since fewer than three distributors reported.
[3] Production began in Mid-1962

Source: "Immunization Against Disease—1972," page 37, Center for Disease Control, PHS, DHEW.

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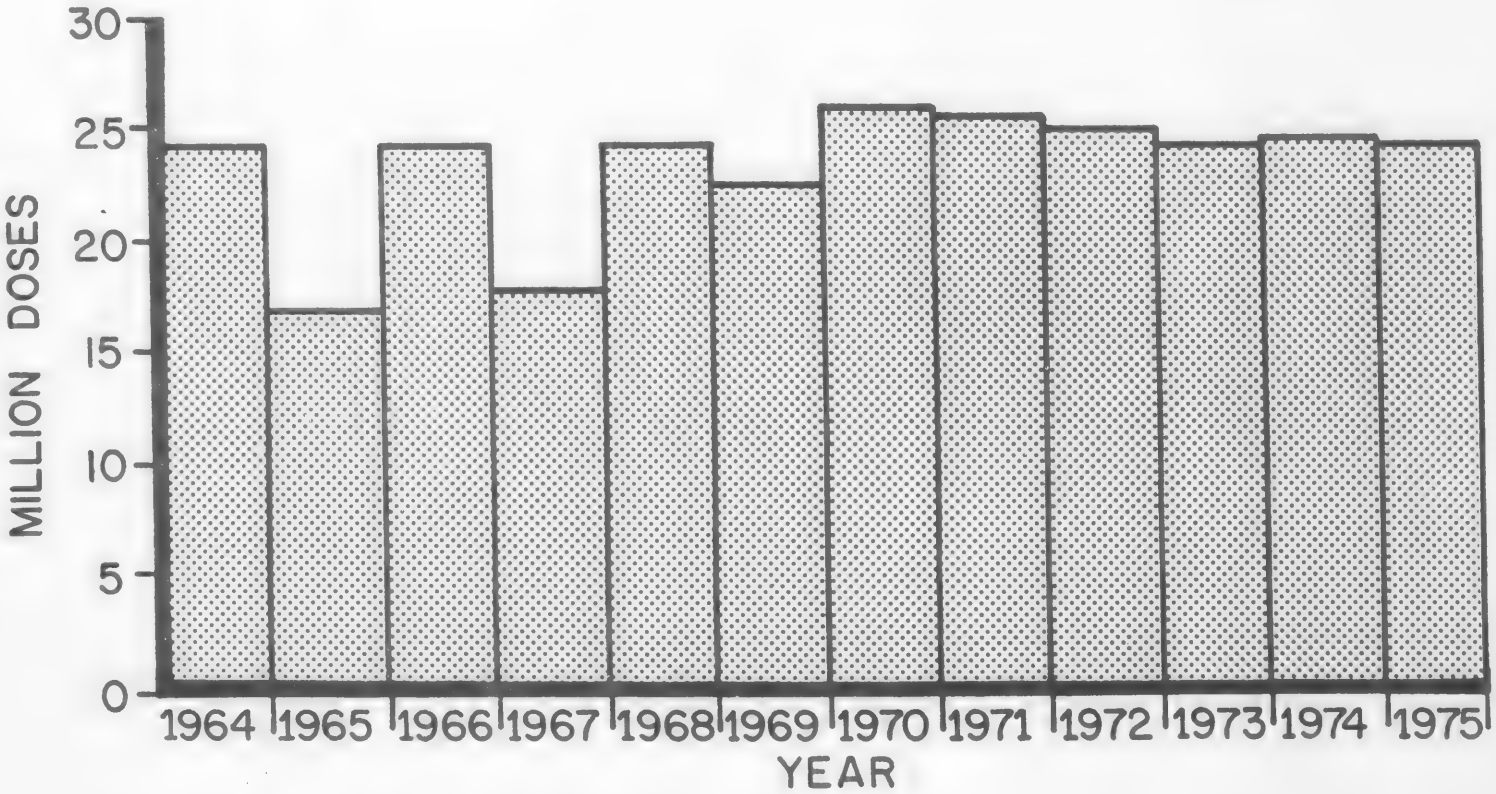
Figure 2A

Net Doses of Trivalent Polio Vaccine Distributed United States-1964-1975



Source: Biologics Surveillance Program

Source: Center for Disease Control, Bureau of State Services, Immunization Division

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In central city populations during 1974, 13.1 percent of children between the ages of 1 to 4 and 9.9 percent of children between the ages of 5 to 9 had never received any type of polio vaccination (Ref. 16).

The 1977 recommendations of the Public Health Service Advisory Committee on Immunization Practices (ACIP) are as follows (Ref. 1):

Rationale for Choice of Vaccine. Although IPV and TOPV are both effective in preventing poliomyelitis, when the benefits and risks for the population as a whole are balanced, TOPV is the vaccine of choice for primary vaccination of children in the United States. The choice of TOPV as the principal polio vaccine in the United States has also been made by the Committee on Infectious Diseases of the American Academy of Pediatrics (1) and a special expert committee of the Institute of Medicine, National Academy of Sciences (2). This is because TOPV establishes intestinal immunity to reinfection, is simple to administer, is well accepted by patients, does not require periodic booster doses, and has a record of having essentially eliminated disease associated with wild polioviruses in this country.

Some countries successfully use IPV, either wholly or in part, to control poliomyelitis. However, because of many differences between them and the United States, particularly with respect to risks of exposure to wild polioviruses and the ability to achieve and maintain very high vaccination rates in the population, their experiences with IPV are not directly applicable here. It is seriously doubted, in fact, based on current achievements in the United States with other injectable antigens, that a sufficient number of persons would regularly be given primary and booster vaccination with IPV to sustain the general level of poliomyelitis protection in the community needed to prevent recurrence of outbreaks.

When considering the immunization of specific individuals, there are occassions when TOPV and IPV are viewed as being alternatives, or when either TOPV or IPV is the specific vaccine of choice, or when both TOPV and IPV may be useful. Prospective vaccinees or their parents should be made aware of the polio vaccines available and the reasons why recommendations are made for giving specific vaccines at particular ages and under certain circumstances. Furthermore, the benefits and risks of the vaccines for individuals and the community should be stated so that vaccination is carried out among persons who are fully informed.

TOPV. Primary immunization. Infants, children, and adolescents through age 18 years: The primary series is 3 doses. The first 2 doses should be given not less than 6 and preferably 8 weeks apart. The third dose should follow in 8–12 months. For infants, the first dose is commonly given at the same time as the first dose of DTP, at 6–12 weeks of age. For older children and adolescents, the third dose may be given as early as 6 weeks after the second if circumstances do not permit the optimal 8–12 month interval.

Adults: Routine polio vaccination of adults residing in the continental United States is not necessary. This is because most adults are already immune, because the risk of exposure to poliomyelitis is generally very small, and because there may be a slightly greater risk of vaccine-associated paralysis among adults than among children receiving TOPV. However, a susceptible adult at increased risk of exposure to infection by virtue of travel to an area where poliomyelitis is common should complete primary immunization with either IPV or TOPV. The schedules are the same as for other age groups.

Supplementary Doses. Entering school: On entering kindergarten or first grade, all children who completed the primary series of TOPV in early childhood should be given a single dose of TOPV. This additional dose will assure immunity to all 3 poliovirus types in the event the original primary series failed to do so. All other children should complete the primary series.

Preadolescent vaccination: A special expert committee of the Institute of Medicine, National Academy of Sciences, reviewing poliomyelitis immunization proposed giving a single dose of TOPV (or completing a full series if required) to children (about 11–12 years old) entering seventh grade. In the committee's view, this supplementary dose could help to assure solid immunity among young adult parents who if susceptible might contract vaccine-associated polio through household contact with infant or childhood vaccinees. The Advisory Committee on Immunization Practices (ACIP) considers the available serologic data to be an insufficient basis on which to recommend routine revaccination of this particular age group. However, the preadolescent years are a good time to evaluate polio immunity and to complete vaccination of those who are inadequately protected. If serologic evidence indicates the value of more generalized revaccination at this time, such an effort could be useful.

Increased risk: Anyone who has completed the primary TOPV series in the past should be given a single additional dose of TOPV when there is a substantial risk of exposure to poliomyelitis, as in traveling. The actual need for this supplementary dose has not been established, but there is value in assuring protection against infection with wild polioviruses when exposure can reasonably be expected.

Pregnancy: Pregnancy is neither an indication for vaccination against poliomyelitis nor a contraindication when protection is needed, as during an epidemic. There is no evidence to suggest that a pregnant woman or her fetus is at greater risk from TOPV than are other persons. (See also, General Recommendations on Immunization, in MMWR 25(44), 1976.)

TOPV-Associated Risk. As indicated above, administration of oral polio vaccines has been associated temporally with paralysis in healthy recipfents and their contacts. Othe: than efforts to identify persons with immune deficiency conditions, no currently available screening procedures can identify those persons likely to experience such an adverse reaction. Although the risk of vaccine-associated paralysis is extremely small for vaccinees and their susceptible family and other close personal contacts, they should be informed of this risk. When the attenuated vaccine strains are to be introduced into a household with adults who have never been vaccinated, some physicians may choose to give these adults at least 2 doses of IPV a month apart, if not the full primary series, before the children receive TOPV. (Vaccination of the children should be assured and not unnecessarily delayed by this process.)

Contraindications. Immune deficiency diseases and altered immune states: Patients with immune deficiency diseases, such as combined immuno-deficiency, hypogammaglobulinemia, and agammaglobulinemia, should not be given TOPV because of their significantly increased risk of vaccine-associated disease.

Furthermore, patients with altered immune states such as those occurring in leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation should not be given TOPV because replication of the vaccine viruses theoretically might be potentiated. When possible, all patients with altered immunity should avoid close, household-type contact with recipients of TOPV for at least 2–3 weeks after vaccination. IPV may be the preferable vaccine for immunizing all persons in this setting. (See also: IPV-Other Uses.)

IPV. Primary Immunization. All ages: Four doses should be given; volume and route of injection are specified by the manufacturer. Of these, 3 doses should be given at approximately 1-to 2-month intervals, and the fourth, 6–12 months after the third. This schedule should be integrated with DTP vaccination begining at 6–12 weeks of age.

Booster doses. A booster dose every 2–3 years has generally been recommended to sustain optimal levels of antibody. It should be noted that this recommendation was developed when the IPV in use was less potent than that available today. As experience is gained with newer IPV products, the recommended interval between booster doses will probable be increased.

The need for IPV boosters could be obviated by supplementing IPV vaccination with primary vaccination with TOPV. In this regard, individuals at particular risk of exposure to poliomyelitis who have received 3 or more doses of IPV should be given at least 1 dose of TOPV, preferably the full primary series.

Other Uses. Children or adults with immune deficiency diseases or altered immune states who are at risk of exposure to poliomyelitis should be vaccinated with IPV. Their antibody responses cannot be assured, but they may derive some protection from vaccination.

Physicians may elect to give a primary series of IPV or, when constrained by time, at least 2 doses 1 month apart to adults who have never been vaccinated ahd who: (1) by reason of travel are at risk of exposure to poliomyelitis or (2) are likely to come in contact with vaccine virus following routine immunization of their children. Less than full

primary immmunization should be supplemented later with the additionally recommended doses.

Precautions. Since IPV contains trace amounts of streptomycin and neomycin, there is a possibility of hypersensitivity reactions in individuals sensitive to these antibiotics.

IPV-Associated Risk. No serious side effects of IPV have been reported.

Case Investigation and Epidemic Control.

The occurrence of a single case of polio should prompt an immediate epidemiologic investigation, including an active search for other cases. if evidence implicates wildpolio virus, a vaccination plan designed to contain spread should be developed. Within an epidemic area, TOPV should be provided for all persons over 6 weeks of age who have not been completely immunized or whose immunization status is unknown.

References

(1) Committe on Infectious Diseases, American Academy of Pediatrics, "Poliovirus Immunization Reexamined," *News and comment,* 27(12 Supp.), 1976.

(2) Nightingale, E., "Recommendations for a National Policy on Poliomyelitis Vaccination," *New England Journal of Medicine,* 297: 249–253, 1977.

A number of aspects of the Food and Drug regulations for manufacture of poliomyelitis vaccine warrant comment, in part to emphasize their importance and in part to raise questions regarding possible revisions.

1. *Poliomyelitis Vaccine, Inactivated (IPV).*—a. *Virus strains.* A manufacturer may employ any virus strain which will give a vaccine that meets the established criteria for safety and potency, but the use of any specific strain may be prohibited whenever the Commissioner "finds that it is practicable to use another strain of the same type that is potentially less pathogenic to man and that will produce a vaccine of at least equivalent safety and potency" (21 CFR 630.1(b)).

The IPV manufactured in this country contains the same strains of Type 2 (MEF–1) and Type 3 (Saukett) polioviruses that were first employed by Salk, and all manufacturers but one have included antigen derived from the Mahoney strain of Type 1 virus, which is highly neurovirulent for monkeys. This manufacturer has, for reasons not indicated in his submission, used the Parker strain of Type 1 virus. The British turned to the Brunenders Type 1 strain after an episode of vaccine-associated disease which involved persistent lived Type 1 Mahoney strain virus. While important changes in the procedures mandated by the regulations make occurrence of similar episodes very unlikely, it would seem reasonable to consider the use of existing known attenuated strains for any IPV that is produced in the future.

b. *Safety.* The regulations reflect concern with both the occurrence of extraneous agents and the persistence of active (live) polioviruses.

(1) *Extraneous microbial agents.* In addition to requirements for testing the "inactivated" monovalent virus pools and the trivalent vaccine for lymphocytic choriomeningitis virus and SV–40, the regulations specify testing each virus harvest or monovalent virus pool, prior to inactivation, for the presence of *Mycobacterium tuberculosis,* B virus (*Herpesvirus simiae*), and SV–40. Fluids from control vessels (uninoculated cultures representing the tissue from which the virus was prepared) may be tested in place of the virus sample.

The Panel recommends that, as well as the tests prescribed on the vaccine itself, the regulations require more extensive testing of control cell cultures, e.g., appropriate observation of control vessels and examination of the control vessel fluids by the most sensitive available methods, on order to exclude the agents named as well as others that might be present in monkey kidney cells (MKC).

(2) *Residual active polioviruses.* The regulations in their present form reflect lessons learned from the earlier episode of vaccine-associated disease. Because of their implications for other products, some of these lessons warrant restatement here.

One is that man, the intended recipient of the "inactivated" product, is a highly sensitive detector of minute amounts of live virus and may well be more sensitive than the available laboratory test systems. In recognition of this, much more stringent tests for active virus were mandated. These included the testing in cell cultures of two sizable and properly timed (see below) samples of each monovalent pool and of the final product in a large number (20) of monkeys. In the latter test, the animals were inoculated by combined intracerebral, intraspinal, and intramuscular routes; in addition, they were given cortisone to enhance susceptibility, and an irritant (procaine penicillin) was injected into the muscle of one limb to simulate the provoking effect seen in man.

A second lesson (enunciated especially clearly by Gard (Ref. 2) is that the curve of viral inactivation becomes asymptotic as the extinction limit is approached and is not a straight line. This makes it impossible to predict precisely from an inactivation curve the time when all the virus will have become inactive. Thus, in addition to tests conducted during the inactivation process (to determine the rate), it is required that two samples (mentioned above) be taken after the estimated baseline time (when 1 milliliter (ml) should contain no more than 1 $TCID_{50}$), the second of which must be taken at least 3 days after the first.

Finally, it was recognized that, when the amount of virus present is exceedingly small, attempts to detect it in any given instance may be unsuccessful. Therefore, occasional vaccine lots which do contain active virus may appear satisfactory because of false negative tests. To insure that the basic procedures routinely employed by a manufacturer do result in complete inactivation (and thus safe lots of vaccine), the rule of consistency was introduced. No lot shall be released unless (1) it is one of five consecutive lots produced by the same manufacturing process, all of which were virus negative and (2) each of the monovalent pools included in the vaccine is similarly one of a series of five consecurive virus-negative monovalent pools of the same virus type.

c. *Potency.* The concept underlying the current potency standard is valid. Vaccine potency is judged on the basis of the titers of antibody elicited in monkeys using a standard multidose regimen reasonably analogous to that recommended for man. Such titers are expressed as the relation of the geometric mean titer (GMT) values (for 10 monkeys) to the titers determined in the same test of reference antisera for each type. A satisfactory vaccine must induce titers which equal or surpass prescribed multiples (different for each type) of the titers of the reference sera. The tests are performed after the final processing, including addition of any preservative (but excluding any adjuvant), with samples from the bulk lots. Dating of vaccine is based on potency tests by the manufacturer on vaccine stored in final packages. This guards against loss of antigen by adsorption to glass container walls, as occurred in the early period of licensure.

Historically, the IPV available prior to the Cutter incident and presumably that used during the Francis trials of the Salk Vaccine, were generally more potent than that produced after 1955, when a requirement for filtration prior to inactivation was imposed. Furthermore, in the post-1955 period, vaccines were acceptable if they induced antibody levels which were two-thirds or more of

the prescribed levels of the reference sera. The regulations governing poliovirus vaccines which were implemented in 1968 required that the concentration of each viral immunotype in the vaccine be increased. However, it is not known how the potency of the one IPV now available (Connaught) compares with that of the vaccine produced in Sweden.

2. *Poliovirus Vaccine, Live, Oral (OPV)*

a. *Virus strains.* The regulations specify criteria for what constitutes acceptable strains and seed virus rather than requiring that only designated strains be used.

The initial crucial criterion for acceptance of an original strain was the demonstration that it be "free of harmful effect upon administration in the recommended dosage to at least 100,000 people susceptible to poliomyelitis, under circumstances where adequate epidemiologic surveillance of neurological illness has been maintained." The present regulations require testing in 1 million subjects for acceptability of new strains (21 CFR 630.10(b)(2)). An accepted set of these strains currently exists with which extensive experience has been gained in this country (as well as elsewhere).

Provision is made for possible replacement of strains, inasmuch as the Commissioner may "prohibit the use of a specified strain whenever he finds it practicable to use another strain of the same type which is potentially less pathogenic for man, and that it will produce a vaccine of greater safety and of at least equivalent potency" (21 CFR 630.10(b)(6)). From a practical viewpoint, assuming that any new candidate strain would have to satisfy the criterion of "one million susceptibles" (21 CFR 630.10(b)(2)), this provision is not very meaningful since nowhere could such a trial be conducted today.

Two properties of the poliovirus vaccine strains are important with respect to safety for man, viz., the neurovirulence for monkeys of the strain per se and the genetic stability of the virus during its replication in the gut of recipients. Although each of the accepted strains displays a satisfactory and comparable low degree of neurovirulence when tested directly in monkeys, experience in the United States with presumed vaccine-associated disease in recipients and contacts of recipients of vaccines prepared since 1961 from these strains suggests that the genetic stability of the respective types is not the same. It is recommended that the problem of genetic stability be critically evaluated and that some thought be given to a more realistic approach to the replacement of the less stable strains. It is suggested that for a strain with an acceptable degree of monkey neurovirulence and, as seen from limited clinical trials in man, more stable "virulence" markers and an equivalent or superior immunogenicity, allowance might be made for authorized (licensed) use of this strain to provisionally replace the current strain. Such authorization should be coupled with a careful monitoring program designed jointly by the Bureau of Biologics and CDC.

The regulations concerning criteria for a seed virus prescribe rigorous scrutiny of monkey neurovirulence and include rescrutiny when a new production seed lot is introduced or when there is evidence of a change in neurovirulence of the production virus.

Provision is made for FDA to supply reference viruses to be used by the manufacturers to control potency (virus titer) and monkey neurovirulence of vaccines. Trivalent and monovalent vaccine lots of all three types are to be compared for potency with reference virus preparations of the corresponding types but, for monkey neurovirulence, the single yardstick is Reference Attenuated Poliovirus, Type 1.

b. *Vaccine production.* The seed lot system is formalized in the provision that virus in the final product may represent no more than five cell culture passages from the original strain, each such passage material having met the criteria established for seed viruses.

The original regulations specified that cultures of kidney cells from only Macaca or Ceropithecus monkeys may be used as the substrate for virus propagation and included generally appropriate and reasonably adequate precautions concerning the selection of monkeys and freedom of the cultures from adventitious microbial agents.

In October 1971, the regulations (21 CFR 631.10(a)) were amended to permit use of human cell cultures as the substrate. This general question is dealt with separately but the stated requirements are of interest. In particular are the requirements that the cell line be capable of producing a vaccine which, by experience in at least 10,000 persons, has been found safe and antigenic; that at least 5,000 of these vaccinees must reside in areas where health-related statistics are regularly compiled by appropriate procedures; and that data adequate to identify the vaccinees be filed with the Bureau of Biologics. The latter requirement is presumably to facilitate uncovering any possible relationship of long-delayed adverse effects to the fact of vaccination.

Provision for long-term followup is a very commendable requirement. However, to date it has not been possible to develop a feasible and economically realistic mechanism for carrying out such a followup. In addition, the specified number is small and would reasonably assure detection of adverse effects with a true incidence of only 1 or more per 1,000. Ideally, for a product that is to be given to millions of individuals, we should be concerned with frequencies at least as low as 1 in 100,000.

c. *Safety and potency.* The basic test for potency is viral infectivity titer and the $TCID_{50}$ content of one dose of vaccine is specified for both MOPV and TOPV. The latter includes different amounts of each viral immunotype.

The regulations prescribed reasonable and generally appropriate measures to exclude unwanted microbial agents (except perhaps Type C RNA containing retroviruses) that might be in the substrate initially or might be acquired by contamination during manufacture. Obviously, these measures should be updated as new technology develops.

Perhaps a more crucial problem has to do with assurances of the safety of the vaccine virus strains themselves which, by selection and mutation, might change character during replication. This problem is dealt with in two ways. Less difficult to interpret is the required test for in vitro genetic markers associated with virulence. These markers should include the rct/40 marker and at least one other. While such markers are in no sense measures of virulence, they do help to identify the strains. The more difficult requirement is the test for monkey neurovirulence. This involves separate groups of monkeys inoculated intrathalamically and intraspinally with each monovalent vaccine lot. The monkeys are observed clinically for paralysis and histopathologically for the qualitative and quantitative presence of poliomyelitis-like lesions, i.e., the grade of severity and degree of dissemination. Observations are compared with similar observations of monkeys inoculated with the Reference Attenuated Poliovirus. A lot is acceptable "if a comparative analysis of the test results demonstrate that the neurovirulence of the test virus pool does not exceed that of the Reference Attenuated Poliovirus" (21 CFR 630.16(b)(1)(iii)).

The verdict of Judge Newcomer (*Griffin* v. *United States*, U.S. Court of Appeals for the Third Circuit, No. 73–1326) makes it clear that an appropriate statistical definition of the phrase "does

not exceed" must be incorporated in the criterion.

We note, however, that the regulations include the principle of consistency in the requirement that each monovalent pool must be one of a series of at least five successive pools that pass the monkey neurovirulence test. When an adequate statistical definition is developed, for example, one with 95 percent confidence limits, it can be expected that 5 percent of the vaccines will fail the test. Therefore, it will be necessary to reevaluate the consistency requirement and redefine it so that it continues to assure vaccine safety without seriously affecting the continuous availability of the product.

Analysis

1. *Efficacy.* The purpose of both IPV and OPV is to prevent the paralytic consequences of infection with polioviruses. Only IPV has been the subject of a rigorously controlled field trial which not only affirmed its relative effectiveness (see below) but established beyond question the protective significance of specific neutralizing antibody. Thus, for checking on the efficacy of specific products, and even of OPV generically, the ability to raise antibody became a valid criterion of efficacy. Additional criteria include the duration of immunity, apparent alteration of epidemiologic patterns, resistance to infection, and the related ability to contribute to development of herd immunity with a possible goal of eradicating wild-type polioviruses from large areas. The generic evidence for efficacy is summarized below.

a. *IPV.* While poliomyelitis vaccine may be regarded as a generic product, there have been changes in the product with time, largely towards higher potency, so that generic experience may not be completely relevant to current products, i.e., it may understate the case. The 1954 Francis trial established that inactivated polio vaccine (IPV) as produced by several manufacturers was relatively effective (90 percent) in preventing paralytic disease. Continued monitoring by CDC of vaccine usage and the vaccination status of reported cases indicate that reasonable protective effectiveness was being maintained. Data for 1959 indicate effectiveness (percent) by age and number of doses of vaccine (Table 3A).

Table 3A.—*Percent Effectiveness*

Age in years	3 doses	4 or more doses
0–4	91	96
5–14	93	96
15–39	82	86
Total	91	95

Nonetheless, in 1959 there were 3,401 reported cases of paralytic disease, of which 750 (14.2 percent) had received three doses of vaccine and 177 (3.4 percent) had been given four or more doses. Failure of high titer homotypic antibody induced by Salk vaccine to prevent paralytic disease in orally infected cynomolgous monkeys suggests that the reason for many, if not most, of the above vaccine failures was not failure to elicit antibody but rather failure to prevent enteric infection, the virus invading the CNS via the nerve fibre (autonomic) pathway rather than the blood stream (Ref. 3). The Swedish experience with ostensibly much more potent vaccine (resulting in virtual elimination of wild polioviruses) suggests that IPV can be highly effective. Over a 2-year period (1969–1970), weekly sewage samples from three Stockholm sewage plants yielded polioviruses on only 11 occasions, all in 1969; on seven of these occasions the virus recovered was Type 3 which is the least immunogenic component of IPV (Ref. 4). Considered in the light of this information, the purification and concentration of the vaccine viruses represent steps in the right direction.

In summary, properly administered IPV reliably induces antibody formation (90 percent to all three types after three doses), is highly effective in preventing paralytic disease, and has clearly altered the epidemiologic pattern of disease in the United States. However, significant numbers of paralytic cases have occurred in adequately vaccinated persons, and, in the United States at least, dissemination of wild-type virus continued with significant frequency (Refs. 5 and 6).

b. *OPV.* There is abundant epidemiologic evidence that subclinical infection with wild polioviruses confers effective, long-lasting protection against paralytic disease. The most compelling points are: (1) In earlier times in this country, the disease, despite the abundant spread of polioviruses, was virtually restricted to very young children (hence the name infantile paralysis) and nearly the entire older population was immune as the result of silent infection acquired early in life. This situation obtains at the present time in the developing countries. (2) In isolated communities, i.e., Alaskan Eskimos, antibody persisted over long periods in the absence of reintroduction of viruses. When virus was introduced, i.e., in Tahiti, it was virtually restricted to individuals born since the particular virus type (Type 1) was last present. There is less abundant, but convincing, evidence that prior infection (reflected by possession of homotypic neutralizing antibody) also affords relative protection against infection in the face of exposure within a household sufficient to infect most nonimmunes. (In the Louisiana families studied, 90 percent of the susceptibles but only 20 percent of the immunes became infected.)

The high frequency of subclinical infections suggests that some, and perhaps many, strains of the wild virus are of low virulence, thus raising the possibility that strains selected for low virulence (or modified in the laboratory) might safely induce an immunity comparable to that arising from natural infection, i.e., protecting against infection as well as disease. Use of such strains as a vaccine should not only protect the recipients against disease but, by making spread of wild strains more difficult, afford indirect protection to those individuals who remain nonimmune. Exploration of this possibility by several investigators, using the behavior of candidate strains in monkeys as a main criterion for selection, was attended with both failure (poor immunizing ability or production of disease in recipients) and success; the latter presently represented by the Sabin strains, whose exhaustive testing in the laboratory was completed in 1957 and 1958.

In considering evidence for the efficacy of the Sabin strains, it must be recalled that an apparently effective inactivated trivalent vaccine developed by Salk had been available and widely used since 1955. The huge field trial which terminated in 1955 established that the Salk vaccine induced formation of neutralizing antibody in a high proportion of nonimmune vaccinees indicating protection against the disease. The proportion of those who developed neutralizing antibodies varied with different lots of vaccine. Subsequent experience appeared to confirm the efficacy of the Salk vaccine, since its widespread use was followed by a dramatic decline in the incidence of paralytic disease. Indeed, based on reasonably accurate estimates of the proportions in each population age group that had received vaccine and the vaccination status of the cases reported, CDC showed that the operational efficacy continued at about 90 to 95 percent for those who had received three or more doses of vaccine. Despite this, a disturbing absolute number of adequately vaccinated persons (three or more doses) experienced paralytic disease (927 cases in 1959 or nearly 18 percent of all cases in that year). We

now know, partly from the Louisiana studies (Ref. 6), that the Salk vaccine then in use (probably much less potent than that produced by Gard in Sweden) induced little protection against enteric infection. We also know from the work of Craig and Brown in 1959 that enteric challenge infection of vaccinated cynomolgous monkeys frequently resulted in paralytic disease despite rather high levels of vaccine-induced antibody (Ref. 3). This suggests the operation of an alternate pathway to the CNS that is unguarded by serum antibody and which probably exists also in man.

Evidence for the efficacy of the Sabin strains needs to be considered in the light of the foregoing experience as well as independently. There has been no large controlled trial of efficacy analogous in scale to the Francis trial of the Salk vaccine. There have been numerous small trials in which the ability to induce antibody in 90 percent or more of susceptibles has been demonstrated for individual monotypic vaccines and for trivalent formulations (these also have served as safety tests, as discussed later). Also, the development of secretory antibodies (coproantibodies) has been demonstrated. Limited followup of children given the vaccine in early clinical trials suggests good persistence of antibody over periods of 6 to 8 years. The stability of the titers suggests that antibody would persist indefinitely.

However, later serologic surveys have revealed a less than satisfactory antibody response and persistence. Relatively poor responses that remain inadequately explained (possibilities include interference due to other enteroviruses and maternal antibody in breast milk) have been encountered among infants in warm climate, developing areas. Studies in Israel suggest that whatever the factors involved, they can be overcome by beginning vaccination at a very early age by using a three-dose regimen of trivalent vaccine routinely and, for lower socioeconomic groups, giving a fourth reinforcing dose later, preferably in the cooler months (Ref. 7). A possibly analogous situation also may exist in the United States. Rasmussen et al. Studied antibody levels in children of low income families in six United States cities, and found that not only had 60 percent received less than three doses (38 percent had received none) but, of those who had received three or four doses, only 28 percent (three doses) or 41 percent (four doses) had antibody to all three viral types (Ref. 8).

The protective significance of neutralizing antibody induced by the vaccine can be inferred from the Louisiana studies (among others) for infection and from the Francis trial (1954) for occurrence of disease (Ref. 9). While no challenge experiments with wild virus strains have been reported, challenges have been done with the vaccine strains by Sabin and others. Although persons lacking homotypic antibody are almost uniformly susceptible to infection, the strains infect few who possess high-avidity antibody, or who have had previous infection with the homotypic vaccine strain. Such reinfection is apparently a function of infecting dose. However, the vaccine strains, as did the wild polio strains in Louisiana, readily infected persons who lacked antibody but who had received the Salk IPV.

Some degree of protective antigenic cross-relation does exist between the three poliovirus serotypes. This crossing occurs between Type 2 and both Types 1 and 3 but not between Types 1 and 3. In this light, the great uniformity with which the Type 2 strain induces antibody (virtually 100 percent) as compared with that to Types 1 and 3 becomes significant. The Francis trial (1954) provided general evidence for the importance of heterotypic immunity by the finding that 64 percent of the virus-positive paralytic cases among controls were in children originally triple negative serologically (only 13 percent of all controls were triple negative). The protective effect of Type 2 virus against Type 1 virus infection was specifically demonstrated in Singapore in 1958 when administration of Sabin Type 2 vaccine was followed by a clear protection against disease in an epidemic due to Type 1 virus (Ref. 10).

Evidence of general effectiveness for protection against disease is derived partly from the very large mass immunization trials carried out in the U.S.S.R. and Central European countries, and also from the virtual elimination after 1963 of paralytic poliomyelitis in the United States as well as other countries following OPV mass vaccination (including Great Britain where the Sabin strain vaccines have replaced vaccines of the Salk type). This is reflected in the "Annual Poliomyelitis Summaries" from which the following data are taken (Refs. 11, 12, and 13). Wide use of OPV began in 1962, a year in which 691 paralytic cases were reported in the United States. This number fell to 336 in 1963, 103 in 1966, 48 in 1968, 33 in 1970, 19 in 1971 including 9 "vaccine-associated" cases (8 in contacts), about which more will be said later, and an all time low of 4 in 1974. All three virus types were nearly equally represented. Effectiveness obviously depends on potency. Although titration of the vaccine strains in susceptible children suggests that the MID_{50} for man is 1 to 10 $TCID_{50}$, the current regulations specify that the dose for each monovalent vaccine contain $10^{5.3}$ to $10^{6.0}$ $TCID_{50}$ and, because of relative differences in competitive interference, the trivalent formulation contain $10^{5.4}$ to $10^{6.4}$ of Type 1, $10^{4.5}$ to $10^{5.5}$ $TCID_{50}$ of Type 2, and $10^{5.2}$ to $10^{6.2}$ $TCID_{50}$ of Type 3 virus.

To summarize, OPV reliably induces the formation of long-persisting serum antibody, enteric secretory antibody, and relative protection against enteric infection, and it clearly protects against disease. That it contributes to eradication of wild-type strains is not readily demonstrable because the vaccine strains induce abundant shedding of virus that is not always unquestionably distinguishable from wild-type strains and because of reversion and the apparent selective advantage of reverted virus, may develop marker characteristics which resembles the wild-type virus. These factors also make it difficult to establish unequivocally a cause and effect relationship on the basis of marker testing of isolates from cases of presumed vaccine-associated disease.

There are important problems concerning the development of poliovirus antibody response of infant vaccines already infected with other enteroviruses. This situation clearly exists in certain economically disadvantaged parts of the world, but its significance in the United States is not known at present.

2. *Safety.*

a. *IPV.* The vaccine-associated disease episode in 1955 focused concern on the need for complete inactivation of the virulent virus strains comprising the viral antigen.

Because of the inherent difficulty in detecting trace amounts of living poliovirus in the vaccine which was made evident by this experience, consistent freedom from detectable virus (in a consecutive series of production lots) is an important safety criterion.

Following the discovery of SV–40 in 1961, tests revealed that certain lots of vaccine produced in the period 1961 to 1963 did contain SV–40 after formalin inactivation. As an interim measure, these lots were further treated with *beta*-propiolactone to inactivate residual SV–40. It is probable, of course, that many lots produced prior to 1961 also contained live SV–40. In 1964, the

regulations required that vaccines be free from SV–40 before formalin inactivation, and tests of the final product in animals and in vitro were modified accordingly.

The question of oncogenic risks associated with SV–40 or other components of the vaccine substrate remains a theoretical concern; to date, however, followup of children in the United States vaccinated with lots known to have contained live SV–40 has failed to reveal any excess incidence of tumors (Ref. 14).

The 1955 episode also led to institution of continuing surveillance by CDC for detection of possible vaccine-associated cases. As criteria CDC used the time of onset after vaccination (4 to 30 days); possible paralysis of the injected arm; and, of special importance, the clustering of suspected cases among recipients of a particular vaccine lot. On this basis, no further cases associated with the use of IPV were recognized, but numerous cases of paralytic disease not meeting all of the above cited CDC criteria did occur within 30 days after receipt of a dose of Salk vaccine. Thus in 1959 there were 259 such cases of which 11 manifested the first paralysis in the inoculated limb (site-correlated). In the 2 succeeding years, the corresponding figures were 116 and 26 total cases with 11 and 2 cases, respectively, site-correlated. These experiences, to a large extent, presumably reflect coincidental occurrence of infection in recently inoculated persons. They also may well include a number of cases directly attributable to IPV by virtue of either the provoking effect of inoculation in an already infected person or even possible residual live virus in the vaccine. From the various reports of product-specific experience, few other reactions of significance were seen including possible hypersensitivity reactions.

The main adverse effect, thus, became vaccine failure, i.e., the occurrence of paralytic disease despite adequate immunization rather than disease induced by vaccination, although the latter, as already indicated, cannot be completely excluded.

b. *OPV.* Generically, safety concerns relate to the vaccine strains themselves (both the original strains and progeny viruses in the vaccine recipients) and to the exclusion of other microbial agents, bacterial or fungal but especially viral. These agents could be introduced by contamination during manufacture, be present in the serum employed in the culture media, or come from the monkey kidney cells used for virus propagation. Recently, this concern has carried over to the use of the WI–38 (human fetal lung) strain of diploid, fibroblastic cells now employed by one manufacturer for viral propagation.

c. *Vaccine virus.* The same vaccine strains are used by all manufacturers and were selected by triple plaque purification in an attempt to obtain genetically homogeneous progeny with a very low order of neurovirulence for monkeys (and hence presumably for man). Progressively larger field trials in man (most relevant being those which involved several million people under 20 years of age in the U.S.S.R., where the age pattern of immunity resembled that in the United States) confirmed the basic acceptability of all three strains with respect to safety for man. However, as suggested by study of numerous isolates from vaccinees, some reversion towards increased monkey neurovirulence does occur during passage in man and conceivably could occur during passage in cell culture. To minimize this possibility and to detect any changes that might occur, the former Division of Biologics Standards (DBS) prescribed certain procedures to be employed by manufacturers. These procedures included use of a seed-lot system (master seed lot, production seed lots, production lots of vaccine) to limit the number of passages to no more than five from the original strains, a series of tests of seed lots and, most important, tests of production lots for level of monkey neurovirulence and possession of certain vitro markers (rct/40 and d) which may be correlated with neurovirulence. This topic was covered in discussion of the FDA regulations. The extensive experience of all manufacturers and of DBS-Bureau of Biologics with the foregoing neurovirulence tests of production lots is currently being analyzed by virus type by the Bureau of Biologics. Such analysis could be the basis for the essential statistical definition of the requirement that the neurovirulence of a production lot cannot exceed that of the reference attenuated virus.

Fortunately, considerable data are available concerning human experience. Early experience with at least one candidate strain (Type 1) in Miami and Berlin raised the specter of vaccine-induced disease—the clinching evidence was recovery of vaccine-like virus from the spinal cord of a fatal case. However, no such episodes were reported in relation to the very extensive trials which preceded approval of the Sabin strains. These strains were approved separately and monovalent vaccines were released as approved, Type 3 being last, in the spring of 1961. By August of that year, it became apparent that in certain areas cases of poliomyelitis apparently related to immunization were occurring following mass use of the Type 3 vaccine. A special advisory committee was formed by the Surgeon General to study the situation. Basically, cases were more frequent in older (20+ years) persons and followed inoculation with Type 3 vaccine, although some also followed Type 1 virus vaccine. There was no association of cases with individual vaccine lots or manufacturers. Surprisingly, there were few documented cases in contacts. In the summer of 1964, at its final meeting, the committee evaluated all suspected cases using the following criteria:

(1) Onset of illness within 4 to 30 days and of paralysis not sooner than 6 days after feeding; (2) significant residual lower motor neuron paralysis; (3) laboratory data not inconsistent with respect to multiplication of the virus fed; (4) no evidence of other motor neuron disease, definite sensory loss, or progression (or recurrence) of paralytic disease 1 month or more after onset.

Several criticisms concerning these criteria are appreciated by the Panel. Nevertheless, using these criteria, the original review, committee identified 57 cases as "compatible" with vaccine association, and CDC has continued to use the same criteria since 1965. A comparison of vaccines employed during those two periods, 1961–1964 and 1965–1972, and the instances of reported cases are summarized in Table 4 (Ref. 13).

Table 4.—*Occurrence of Vaccine-Associated Cases of Poliomyelitis According to Vaccine Virus Type and Vaccination Intervals*

Class of patient (time)	Vaccine administered				
	Type 1	Type 2	Type 3	Trivalent	All
Recipients:					
1961 to 1964	[1] 16 [2] (0.15)	2(0.02)	39(0.37)	5(0.18)	62(0.18)
1965 to 1972	1(0.11)	0	6(0.81)	9(0.05)	16(0.08)
Contacts:					
1961 to 1964	0	0	3(0.03)		3(0.01)
1965 to 1972	2(0.23)	2(0.29)	0	[illegible](0.30)	42(0.20)

[1] Number compatible cases.
[2] Incidence (cases per million distributed doses).

More recent CDC data (M. Gregg, presented August 11–12, 1975 at the American Academy of Pediatrics) extend through 1974 and add five recipient and eight contact cases (all TOPV related). During 1965–74, 151 million doses of vaccine were distributed. Hence, the frequency of adverse reactions in this period remained at one event (recipient or contact) per 4.8 million doses distributed although, with the advent of TOPV, the ratio of contact to recipient cases has increased to 3.3:1.

Proper interpretation of the 83 recipient cases and the 53 contact-associated cases is seriously complicated by several factors: (1) Only monovalent types of OPV were used in the 1961 to 1964 period; subsequently, primarily trivalent OPV has been used. (2) A major use of MOPV in the 1961 to 1964 period was as a part of mass vaccination campaign in locations where abundant wild-type virus was still present. (3) Since 1965, the vaccine (chiefly TOPV) has been used in public health immunization campaigns and by private physicians in their practice. (4) According to data presented to the Panel by the Bureau of Biologics, vaccines prepared and administered from 1965 to the present are comprised of virus strains with significantly lower neurovirulence potential than earlier strains. (5) Although there were remarkably few vaccine-associated cases (136 through 1974 or about 1 per 4 million distributed doses of vaccine), many were incompletely analyzed and include an unknown proportion representing disease in immunodeficient children. (6) Adults, who were a major source of recipient cases in 1961 to 1964, have not been routinely immunized since 1964.

With these reservations, the following statements can be tentatively made. Administration of trivalent OPV is associated with less than one "compatible" case among recipients per 15 million doses (or, including contacts, less than 1 per 4.8 million doses), and omission of individuals with altered immune status would probably reduce this rate even further. The special vulnerability of immunodeficient children to vaccine virus infection will be emphasized in a forthcoming CDC report. Finally, an analysis of the contact-associated cases occurring since 1965 reveals that these cases are nearly equally distributed between Type 2 and Type 3 strains, thus suggesting a previously unappreciated instability to Type 2 virus with respect to neurovirulence.

d. *Vaccine substrate.* Procedures for the exclusion of extraneous agent from production lots depend on the cells used for virus propagation, i.e., primary monkey kidney (MKC) or WI–38. For MKC, the monkeys used are observed in quarantine to insure general good health and, by specific test, freedom form tuberculosis. The initial unit of production is the pair of kidneys from one animal. Tests for specific agents are conducted separately in parallel on cell culture fluids removed immediately prior to virus inoculation, on fluids from control cell cultures held an additional 14 days, and on viral harvests from inoculated cultures. These include cultures for various bacteria and mycoplasma; observation of the control cultures for possible nonpoliovirus effects (cytopachic effect (CPE), hemadsorption, interference); subinoculation into various monkey, human, and rabbit cell cultures to exclude known simian agents, including SV–40, pox viruses, *Herpesvirus simiae* (Bvirus), and measles virus; and inoculation into adult and suckling mice and into rabbits and guinea pigs to exclude coxsackie-viruses, LCM virus,other neurotropic viruses, *Herpesvirus simiae* (B virus) again, and tubercle bacilli. All these tests involve the use of specified (large) sample of the production material (commonly 500 doses or 50 ml, whichever represents the greater volume).

Despite these specified precautions, the question of the presence of contaminating viruses in nonhuman primate substrates persists. The safety record is clear in terms of at least 15 years of followup. However, it might be suspected that viruses such as papovaviruses (other than SV–40), cytomegaloviruses, foamy virus, C type viruses, and perhaps other unknown viruses of primates could theoretically be present in a vaccine and not be detected by test methods currently prescribed by regulations. The presence of any such viruses would be clearly undesirable even though no increase in oncogenic risk to vaccines has thus far been detected. The principal theoretical advantage of vaccine produced in MKC culture is its freedom from human genetic material. The principal practical advantage is the 15–year record of safety associated with its use.

Recent amendments to the regulations allow production of vaccine in an approved strain of human cell cultures (in this case, WI–38 cells) which are identified by historical records; shown to be free of oncogenic properties and of adventitious microbial agents; and shown capable of producing a vaccine which, by experience in at least 10,000 persons, has been found to be safe and antigenic. Cell cultures used for vaccine production must be monitored karyologically and shown to fall within 95 percent confidence limits of the status of the original cell strain. Cultures are also checked for CPE before inoculation, and growth fluids tested in monkey, rabbit, and primary human cell cultures are checked for possible adventitious agents. Uninoculated control cultures (25 percent of a production batch) are similarly observed and further checked by hemadsorption and inoculation into embryonated eggs. The actual viral harvests are then checked in a manner similar to that prescribed for MKC viral harvests.

Introduction of a human diploid celline as the vaccine substrate raises two questions, one relating to the vaccine viruses and the other to transmissible effects of the substrate. While the Pfizer experience suggests that virus in production lots of vaccine is of acceptable neurovirulence (i.e., meets the requirements specified in the regulations), the information on reversion rates for virus so produced is not adequate. As detailed in the review of the Pfizer submission, vaccine

progeny virus shed by vaccinated children proved reasonably stable with respect to rct/40 and d markers but showed a clear trend towards increasing monkey neurovirulence over time ("early" versus "late" isolates), especially in the case of Type 2 and Type 3 virus isolates. While a similar trend has been observed with the progeny of MKC produced vaccine strains, direct comparison of the magnitudes of change would be desirable. Another question, so far unexplored, is whether poliovirus vaccines cultivated in WI–38 cells contain human DNA or RNA and, if so, what the signficance might be. The question of genetic stability has been raised previously, but the effect of the substrate upon genetic reversion after gut passage is a subject for further study. There is as yet no information that will allow comparison of the stability (rct/40 and d markers as well as monkey neurovirulence) of vaccine virus progeny shed by children fed virus propagated in WI–38 and those fed virus propagated in MKC.

As mentioned earlier, the WI–38 cell line has been widely studied in terms of karyotype, presence of adventitious agents and tumorigenic potential. All of the data available to date indicate that the line is "safe" in terms of its use in vaccine production although, as with any candidate cell substrate, one can pose a number of theoretical risks.

Thought should be given to the future availability of WI–38 cell stocks as well as to any problems which might arise and preclude the use of WI–38 cell stocks for vaccines. Since large volumes of cells are required in producing bulk lots of vaccine, and since the WI–38 strain enters the early phase of senescence at about population doubling level (PDL) 31–33, cultures for production must be initiated with low passage stock. PDL 8 material represents the lowest level available, and hence the current supply of low passage WI–38 cells represents a finite resource.

For these reasons the Panel recommends that the Bureau of Biologics continue its programs on the development of candidate cell lines which can serve as alternative to WI–38. Based on broad experience with WI–38 cells, it is recommended that efforts be directed toward the development of a similar human cell line. However, since characterization of a new cell line is a time-consuming, complex procedure requiring years of work with no guarantee of success, other options should be exercised, such as continued studies to characterize the diploid fetal rhesus lung line developed by the Bureau several years ago. While cultures of this type have not been used for vaccine preparation, they merit consideration. Use of the WI–38 (and potentially other lines) of human diploid cells as an accepted viral substrate for vaccines greatly improves the safety aspects of OPV in that the possibility of adventitious agents endogenous to the substrate are greatly reduced. Furthermore, the uniformity or consistency of the WI–38 cell line in PDL 20–29 provides the most thoroughly evaluated cell substrate employed for human viral vaccines. To date no adventitious human viral agent has been recovered from these cells. Also, live virus vaccines, including OPV, produced in these cells have been administered to hundreds of thousands of persons with no recognized adverse effects. However, it is possible that infrequent acute complications might have been missed or that possibly more frequent complications with long latent periods (over 10 years) would not yet be apparent.

The theoretical long-term oncogenic or latent virus risk of WI–38 cells has been particularly criticized. It should be noted that there is little evidence that viruses homologous to a host species are more virulent for that host than viruses from a heterologous host, whereas the opposite has been observed, e.g., monkey B virus in man and SV–40 in hamsters. Except for the unexpected occurrence of clustered untoward reactions, the risk from vaccines produced in WI–38 (or other human cell strains) will be known only from carefully organized, large-scale prospective studies designed to detect low incidence complications. The problems of conducting such studies have already been commented upon.

3. *Benefit/risk.* The considerations here are all generic rather than product-specific. Prior to the advent of Salk vaccine, the incidence of paralytic poliomyelitis was clearly rising and had reached about 25,000 cases. In 1971 the actual number was 17, including 9 "vaccine-associated" cases (8 of which were in contacts). None of these occurred in persons with a history of adequate vaccination. This compares with 3,400 cases in 1959 (when Salk vaccine had been widely used since 1955) of which 18 percent (over 900 cases) were in persons who had been adequately vaccinated. Based upon the experience with United States licensed vaccines, either type is highly beneficial. However, oral vaccine is clearly superior to Salk vaccine, despite an overall risk (contacts included) of about 0.2 case per million distributed doses of vaccine. Further comparisons would require comparison of age-specific risks of the vaccinees and their contacts with the projected similar risks in the total population, had no vaccine become available. This probably would show a great benefit among children and some among adults for whom the risk of contact-acquired vaccine infection with disease seems to be greatest. It would be important to know just what the risk to contact adults is, since it may be greater than the risk they would experience as vaccine recipients.

4. *Labeling.* Labeling should conform to FDA's regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

Recommendations.

1. *IPV.* In light of the current limited availability and use of IPV, the Panel recommends that, if there is a continued demand for the product, consideration should be given to making changes in Federal regulations governing manufacture of IPV as follows:

a. It would be prudent if virus strains employed to produce IPV were of low neurovirulence.

b. The feasibility of propagating vaccine virus in human diploid cell should be explored.

c. Comparative testing of vaccines licensed in the United States and of those currently in use in Europe should be undertaken to determine the relative potency of these products. The United States potency standards should then be reevaluated in light of these results.

d. The package inserts should state the indications for IPV and relate these indications to those recommended for OPV.

e. Manufacturers who have not produced IPV for 2 or more years should again be required to demonstrate their capability to produce a satisfactory product before new vaccine lots are released.

2. *OPV.* a. The Panel suggests that PHS should consider revising their recommendations for use in terms of the following:

(i) The Panel sees no reason to continue recommendation of MOPV as an alternative method for routine immunization. MOPV is most logically used to combat epidemics of known virus type and inserts of any MOPV should reflect the use.

(ii) Risk of disease, given poliovirus infection of a nonimmune person, is age-dependent and is greater for adults than for children. Risk of disease due to virus of vaccine origin is greater for those infected by contact (because of possible virus reversion) than for vaccinees. With

routine immunization limited to children, most vaccine virus infections in adults will be contact-acquired and, logically, be most frequent among nonimmune adults. While the magnitude of the related risk of disease is not precisely known, the Panel believes that unimmunized parents of children undergoing OPV immunization should be included among the adults for whom TOPV is recommended.

(iii) Vaccinees should be informed of the occurrence of fecal shedding of virus and the related potential for spread of infection should be emphasized together with appropriate precautions to minimize such spread. (See also (ii), above.)

(iv) Since wild enterovirus infections existing at the time of vaccine feeding may, by interference, prevent immunizing infection, the recommendations should indicate that when circumstances do not dictate otherwise, OPV for other than infant immunization should be administered when enterovirus prevalence is usually low (perhaps November through June).

b. Several issues concerning neurovirulence of the vaccine virus strains should be resolved.

(i) PHS regulations should be revised after the analysis being carried out by the Bureau of Biologics has been completed to include an appropriate statistical definition of the requirements for interpretation of the neurovirulence test of vaccine lots.

(ii) The Panel is concerned with the apparent genetic instability of the currently licensed poliovirus strains employed in TOPV. The Bureau of Biologics should give consideration to developing a program that will attempt to resolve current problems and eventually permit the selection of strains for licensing which are adequately immunogenic, of acceptable low neurovirulence, and of maximum genetic stability with respect to neurovirulence.

This problem has both practical and theoretical aspects. On the practical side, the potential future nonavailability of primates for the critical testing of neurovirulence makes it imperative to identify in vitro marker correlates of neurovirulence. On the theoretical side, possibly related to its review of the statistical evaluation of monkey neurovirulence tests, the Bureau of Biologics should support research to better understand the genetic basis of attenuation.

(iii) To make substitution of strains possible, the criteria for strain acceptability in the Federal regulations should be modified. Emphasis should be given to the importance of documentation of the monkey neurovirulence characteristics of the strains and to definitive characterization of the genetic stability of strains recovered after gut passage in intensive, carefully conducted clinical trials, supplemented by intensified postlicensing surveillance during the year or two after the vaccine is first released. These requirements would be more attainable and more meaningful than the current requirement to test in 1 million susceptibles.

c. Review of problems relating to the virus substrate lead the Panel to the following recommendations:

(i) A technical workshop should be convened to evaluate the relative merits of simian and human cell substrats for viral vaccine production. This should be composed of presently active investigators representing expertise in virology, cell culture karyology, immunology, and epidemiology. The apparent merits of the human cell substrates clearly imply an advantage over simian or other primary cell substrates and, if this advantage is valid, only human cell substrates should be employed. The workshop should consider in detail the actual and theoretical risks of the two types of substrate and what, if any, research should be sponsored by the Bureau of Biologics to resolve the issue.

(ii) PHS regulations governing tests for adventitious agents should be revised to insure that full advantage is taken of new methodology as it evolves for detecting such agents as well as foreign nucleic acids or proteins.

(iii) As part of the overall vaccine surveillance effort, large (100,000 or more) comparison groups of recipients of vaccines produced in diploid and in simian cell substrates, should be identified for followup.

d. The Panel strongly urges that legislation be enacted to provide reasonable compensation to the injured person, and protection of the manufacturers against liability, in cases of adverse effects attributed to licensed vaccines produced in accordance with PHS regulations and properly administered (see Preface and Introduction).

Review of Individual Poliomyelitis Vaccine Products

Poliomyelitis Vaccine (Purified) Manufactured by Connaught Laboratories, Ltd.

1. *Description.* The vaccine is prepared according to the method of Salk. It is a suspension of the three types of poliovirus, Type 1 (Mahoney strain), Type 2 (MEF strain), and Type 3 (Saukett strain), which are grown in monkey kidney cell cultures and inactivated with formalin. The vaccine is purified and reconstituted to contain approximately twice the original concentration of virus antigen. It contains no more than 200 micrograms (mcg) of streptomycin and 7 mcg of neomycin per ml. It contains no serum.

a. *Recommended use.* For the prevention of poliomyelitis.

(1) *Precautions.* Vaccination should be deferred in the presence of active infection, acute respiratory disease, and during the course of steroid or other immunodepressant therapy. It should not be given to individuals sensitive to streptomycin and neomycin.

(2) *Caution.* Discard any vaccine which is not perfectly clear and cherry red in color.

(3) *Adverse reactions.* There are remarkably few, but it is always possible that the recipient may be highly sensitive to a vaccine component, hence it is advisable to have epinephrine 1:1000 available.

(4) *Dosage and administration.* The vaccine is given in 1 ml doses, subcutaneously or intramuscularly. The regimen is a series of 3 doses separated by 4 or more weeks and a booster dose given 6 to 12 months after the third dose. Recall doses every 2 to 3 years are recommended.

b. *Contraindications.* No contraindications are stated as such.

2. *Analysis.* a. *Efficacy.* The general evidence for efficacy of IPV is presented in the generic review.

The manufacturer's data provides convincing evidence that given to infants 2½ to 4 months of age, the vaccine alone or in any of several combinations (DPT, DT, T, DP, Measles) will induce an antibody response to all three poliovirus types in about 97 percent of individuals with a titer of 1:16 and in 89 percent of individuals with a titer greater than 1:16. Evidence also is presented to show that a satisfactory proportion of the Canadian population possesses antibody to all three types, presumably attributable largely to widespread use of IPV and that, at least in Ontario, paralytic disease has fallen to a very low level, from 0 to 2 cases per year since 1962. (This observation alone, however, does not firmly establish IPV efficacy since OPV is also used.)

b. *Safety.* The safety of IPV generically is discussed elsewhere. Review of the manufacturer's data indicates that the Connaught Laboratories, Ltd. vaccine has been rigorously tested and that the methods employed consistently give a product free from any detectable (by the tests employed) viable microbial agents including poliovirus as well as SV-40

virus and other adventitious agents. Apropos SV–40, kidney cells from only Cercopithecus or Cynomolgous monkeys are used.

c. *Benefit/risk.* This discussed in the generic statement.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of the ACIP. The summary under the heading indications and usage should include indications for preferring IPV and OPV.

3. *Conclusions.* a. *Critique.* In general, the submission is adequate. The procedures, etc., are clearly described, and the necessary documentation on use of the vaccine in man has been provided. Several specific comments, however, seem cogent:

(1) Vaccine seed pools are defined but the history of the virus strain from the time of its isolation should be given. Of all the manufacturers considered in this review, Connaught Laboratories, Ltd. demonstrates the highest concern for seed pool characterization and identification. However, reliance on a complement fixation test for strain identification rather than virus neutralization should not be encouraged.

(2) Because of the details provided by Connaught in its submission, which could well serve as a model, this vaccine is comparatively easy to evaluate.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness.

Poliomyelitis Vaccine Manufactured by Cutter Laboratories, Inc.

This product has not been manufactured for a number of years and the only way to assure that competence for its production exists, and to guarantee its safety and efficacy, is to require a new submission when and if Cutter laboratories, Inc., desires to resume marketing of this vaccine. It is recommended that 21 CFR 601.5 be invoked, whereby the Commissioner may recommend that a license be suspended or revoked upon finding that "manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made."

Furthermore, if the manufacturer proposes to resume production, the Panel recommends that this product be placed in Category IIIB and that appropriate license(s) be revoked pending completion of additional testing and conformance with the recommendations of this report because there is no evidence presumptive of safety or effectiveness for this product.

Poliomyelitis Vaccine (Purivax) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

This product has not been manufactured since 1965, and the only way to assure that competence for its production exists, and to guarantee its safety and efficacy, is to require a new submission when and if Merck Sharp & Dohme, Inc. desires to resume marketing of this vaccine. It is recommended that 21 CFR 601.5 be invoked, whereby the Commissioner may recommend that a license be suspended or revoked upon finding that "manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made."

Furthermore, if the manufacturer proposes to resume production, the Panel recommends that this product be placed in Category IIIB and that appropriate license(s) be revoked pending completion of additional testing and conformance with the recommendations of this report because there is no evidence presumptive of safety or effectiveness for this product.

Poliomyelitis Vaccine; Poliomyelitis Vaccine, Adsorbed Manufactured by Parke, Davis & Co.

These two products have not been manufactured for some years and the only way to assure that competence for their production exists, and to guarantee their safety and efficacy, is to require a new submission when and if Parke, Davis & Co. desires to resume marketing of these vaccines. It is recommended that 21 CFR 601.5 be invoked, whereby the Commissioner may recommend that a license be suspended or revoked upon finding that "manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made."

Furthermore, if the manufacturer proposes to resume production, the Panel recommends that this product be placed in Category IIIB and that appropriate license(s) be revoked pending completion of additional testing and conformance with the recommendations of this report because there is no evidence presumptive of safety or effectiveness for this product.

Poliovirus Vaccine, Live, Oral Trivalent, Orimune; and Poliovirus Vaccine, Live, Oral, Types 1, 2, and 3 Monovalent, Orimune Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This description is taken from the package insert.

Trivalent is a mixture of three types of attenuated polioviruses which have been propagated in Cercopithecus monkey kidney tissue culture. The cells are grown in the presence of a nutrient medium consisting of Earle's balanced salt solution containing lactalbumin hydrolysate, antibiotics, vitamins and calf serum. After cell growth, the medium is removed and replaced with fresh medium containing the poliovirus inoculum but no calf serum. The final vaccine is diluted: with sorbitol solution for use in a 2 ml dose; with modified tissue culture maintenance medium containing sorbitol for use in a 0.5 ml dose; and with modified tissue culture maintenance medium for the use in the 2 drop (0.1 ml) dose.

Each dose (whether 2 ml, 0.5 ml or 2 drops) contains less than 5 micrograms of streptomycin, neomycin and mycostatin.

Potency is expressed in terms of tissue culture infective doses ($TCID_{50}$) of virus contained in the recommended vaccine dose. The approximate $TCID_{50}$ of each strain of poliovirus in a human dose is as follows: Type 1—800,000; Type 2—100,000; and Type 3—500,000.

The description for the monovalent vaccines differs from the above in that it refers to the specified virus type; states the limit of each antibiotic per dose to be 1 microgram; and, for each type, the virus content to be 200,000—1 million $TCID_{50}$ per dose.

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.* a. *Efficacy.* This is covered in large part in the generic review. Lederle Laboratories has complied with the licensing requirement (21 CFR 630.11) that five consecutive production lots of each monovalent vaccine be tested in susceptible persons and that each lot elicit serum neutralizing antibody in at least 80 percent of recipients after one dose. The results were as follows:

Table 5.—*Neutralizing Antibody Response to Monovalent OPV*

Preimmunization antibody titer	Antibody response to viral type					
	Type 1		Type 2		Type 3	
	Number of vaccinees	Seroconversion [1]	Number of vaccinees	Seroconversion [1]	Number of vaccinees	Seroconversion [1]
<1:4	141	89.3	134	91.0	182	[illegible]
1:4 or 1:8	[illegible]	[illegible]	71	97.1	[illegible]	[illegible]

[1] Percentage of group seroconversion.

For trivalent vaccine, the Biologic Regulations prescribe that after the required feeding regimen, each of five consecutive production lots must attain in susceptible individuals a seroconversion rate of at least 99 percent for each of the three viral types. Again, Lederle Laboratories has complied with this requirement; of 422 children with no antibody to any of the three virus types, seroconversion after two feedings of vaccine was 90.4 percent for Type 1, 99.7 percent for Type 2, and 98 percent for Type 3. A third feeding raised the proportion of seroconversions to Type 1 to 98.3 percent. They also showed that preexisting enterovirus infection had some inhibitory effect on infection with polivirus vaccine. In populations which included children possessing antibody to one or two serotypes, similar seroconversion rates were observed to the lacking type.

Finally, in a followup of these trials it was found that antibody persisted for over three years in a high proportion of vaccine recipients.

Table 6.—*Persistence of Antibody Induced by Oral Poliomyelitis Vaccine*

Postvaccination interval	Percentage of individuals with antibody to:		
	Type 1	Type 2	Type 3
One years	90.0	100.0	96.7
Two years	90.0	100.0	94.5
Three years	81.3	100.0	94.5

b. *Safety.*

(1) *In vivo and in vitro tests.* The Lederle Laboratories submission consists of detailed descriptions of the various test procedures (in the original licensing submission and amendments) and a sample protocol for a lot of Type 1 virus said to be representative of all protocols (including these for Types 2 and 3) submitted to FDA. Also included were sets of review information, one set each for single monovalent lots and one for a trivalent lot formed from the same three monovalent lots. Thus actual data were provided for two lots of Type 1 virus, one each of Type 2 and Type 3 viruses, and data for one lot of trivalent vaccine. The reported testing was amply documented and appeared in all cases to have yielded satisfactory results, including the crucial monkey neurovirulence test. The most troublesome and least stable strain of poliovirus for all manufacture is Type 3. Examination of the data submitted for the single lot of Lederle Type 3 virus tested showed that its apparent neurovirulence was less than that of the Type 1 reference vaccine. Later data submitted by the Bureau indicated that testing of five successive lots of each type had indicated acceptable low neurovirulence for all.

(2) *Information on vaccine recipients.* Individuals included in the field trials mandatory for licensure were observed for possible immediate adverse effects. None of significance were reported.

(c) *Benefit/risk.* See generic discussion.

d. *Labeling.* Labeling should conform to the FDA's regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions.*

a. *Critique.* The principal defects in the submission are a lack of information on range of variations encountered in the monkey neurovirulence tests of successive vaccine lots, especially Type 3, (the desired data was later furnished by the Bureau) and the failure to report product-specific adverse experiences. The generic monovalent and trivalent vaccines are effective, useful, and safe. These products are acceptable examples of the generic vaccine.

b. *Recommendations.* The Panel recommends that these products be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for these products.

Poliovirus Vaccine, Live, Oral, Trivalent, (Diplovax) Manufactured by Pfizer Ltc.

1. *Description.* Diplovax is a mixture of monovalent (Types 1, 2, and 3 Sabin strains) vaccines propagated in a human diploid cell line (WI–38 Hayflick); each dose contains approximately 800,000 Type 1, 100,000 Type 2, and 500,000 Type 3 $TCID_{50}$.

The WI–38 strain of human diploid cells represents a cell line propagated by repeated serial passage. It has been shown to be free of any known adventitious agents by extensive testing.

Further statements in the labeling indicate that the vaccine strains, manufacturing methods, and testing comply with the PHS requirements. Lactalbumin hydrolysate medium is employed in the tissue culture host system for viral propagation. Potency is expressed in terms of $TCID_{50}$ with ± 0.5 log accuracy and the meaning of this term is explained. Sucrose is added to the vaccine as a stabilizer and inclusion of phenol red gives the vaccine a variable red color. If the color of an entered vial changes from red to yellow on storage, bacterial contamination should be suspected and the vial discarded.

Also included in the description is the following statement of vaccine action:

> Usually, both a systemic and local response are produced. A systemic response involves production of serum or humoral antibodies which help protect the individual against clinical poliomyelitis infections. A local response is one in which resistance to further infection by the same virus type is produced in the intestinal tract. The resistance to further infection may reduce the incidence of temporary carriers, individuals who harbor and disseminate naturally-occurring wild poliovirus although they may show no clinical symptoms of infection.

a. Recommended use. See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.*

a. *Efficacy.* Basic to efficacy is potency. Assay data for 10 filling lots (derived from a single large lot) indicate that all contained the requisite amounts of virus of each type. Also, in the review information submission, data were included to show the stability of potency for each virus type during 6 months of storage at 4° C and for one year at −20° C.

Also included were data on the response in seronegative children given monovalent vaccines (five consecutive production lots of each type) and trivalent vaccine (also five consecutive lots). For comparison, previously acquired data for vaccine produced by this manufacturer in MKC are also presented in the submission. Single feedings of the monovalent WI–38 diploid cell-produced vaccines resulted in satisfactory seroconversion for all viral types (Type 1, 92.3 percent; Type 2, 90.6 percent; Type 3, 88.9 percent) based on studies of from 144 to 191 children. Trivalent feeding (three dose series) of 100 children negative for antibody to all three viral types resulted in higher rates, viz., 96, 99, and 94 percent, respectively.

These results are equivalent or superior to the earlier ones with MKC vaccine prepared by this manufacturer. Otherwise, the case for efficacy is based on the aggregate generic experience with the Sabin strains of poliovirus.

b. *Safety.* This submission includes a summary brochure on the comparative virtues of WI–38 human cells versus primary monkey kidney cells, and a Pfizer-produced pamphlet which describes the WI–38 cell strain and its use in vaccine production. The pamphlet contains pertinent references on the subject. The essence of the presentation is that the WI–38 cell strain constitutes a single cell source for which a 20-year reservoir exists, and that it has undergone considerable scrutiny for adventitious agents and undesirable (e.g., oncogenic) properties, all with negative results. Recent evaluation of the situation regarding supply put in question the 20-year availability of the cell strain.

Also included are data concerning the characteristics of the vaccine progeny virus shed by the children given the monovalent vaccines. Data on the rct/40 marker are given for isolates grouped by time since feeding but they show no consistent trend related to increasing time between feeding and viral recovery (intervals 1–22, 23–42, and 43 or more days). The results, combining all time intervals, are shown in Table 7.

Table 7—*Distribution of rct/40 Markers of Progeny Virus Shed by Children Given Monovalent OPV*

Poliovirus	Percentage of isolates with rct/40 marker		
	t–	t±	t+
Type			
1 [1]	78	22	0
2 [2]	43	54	3
3 [3]	34	66	0

[1] 125 isolates.
[2] 124 isolates.
[3] 59 isolates.

There was least shift in marker characteristics with Type 1 virus, but the few rct+ isolates were all Type 2. These data are said to closely parallel similar data on progeny virus shed after feeding vacine virus grown in monkey kidney cells. Tests for the d marker were made on 137 isolates (all three types were represented). Since none indicated a shift from d (virus grows poorly under low concentrations of bicarbonate) to d+ (virus grows well under low or high bicarbonate concentrations), this test was discontinued in the evaluation of shed virus.

Some of the isolates, representing viral recoveries made both early (first 2 weeks) and late (3 or more weeks) after feeding the vaccine, were tested by intracerebral inoculation in monkeys using first cell culture passage fluid (undiluted) and two monkeys per isolate. The results are summarized in Table 8.

Table 8—*Results of Tests for Neurovirulence of Progeny Virus Shed by Children Given Monovalent OPV*

Virus type	Viral isolate	No. of monkeys	Percent of monkeys showing		
			Negative for lesion and/or paralysis	Histologic lesions	Paralysis
1	Early	13	77	23	0
	Late	31	45	35	6
2	Early	78	80	31	0
	Late	62	32	64	78
3	Early	14	86	71	36
	Late	41	10	90	54

The submission concludes that:

Although there is some evidence of increased neurovirulence for monkeys in the later specimens of virus of all three types, the pattern follows that which has been seen and extensively reported in the literature for monkey kidney vaccines. It also should be pointed out that 10 of the Type 3 specimens had titers greater than 10^6 $TCID_{50}$ per dose, i.e., 10 times that which is used in the standard neurovirulence test. It is our view, therefore, that preparations of the vaccine in human diploid cells instead of monkey kidney tissue has not resulted in any significant change in the biological characteristics of the vaccine viruses.

It is unfortunate that parallel concurrent studies were not done with vaccines produced in MKC.

Other than data on the potency and animal safety of the final containers of trivalent vaccine from 10 filling lots, the only data on in vitro and animal testing of production lots are those for five consecutive lots of monovalent Type 1 vaccine. These covered tests in eggs; hemadsorption on control cultures; chromosome studies; tumorigenicity (comparing WI–38 cells with HEP–2 cells in adult mice); and tests in suckling and adult mice, guinea pigs, rabbits, mycoplasma medium, other bacteriologic media, human embryonic lung cells, human embryonic kidney cells, vervet monkey kidney cells, and rabbit kidney cells, all for possible adventitious or contaminating agents. The material tested included control cultures, fluids representing medium changes (from production cultures), fluids from control cultures, and the actual virus-harvest fluids. All such tests were judged satisfactory. Similar data for consecutive lots of Types 2 and 3 were later supplied by the Bureau of Biologics. However, it should be noted that in the past occasional lots had to be discarded because of bacterial or fungal contamination, and that in two instances batches of WI–38 cells being built up to passage 29 (that used for vaccine production) had to be discarded because of contamination with attenuated polioviruses of still unknown origin. Since then, the manufacturing procedures were modified (in 1972–1973) and the problem has not recurred.

Tests on the vaccine virus itself were the same as those prescribed for MKC vaccine which incorporated in vitro markers (rct/40 and d), identity of the virus, and its neurovirulence in monkeys. These five lots of Type 1 virus were tested in parallel with reference lots of Type 1 virus. Careful comparison fails to reveal significant variation of results between test lots of vaccine or between test and reference lots and thus for Type 1 vaccines points to a desirable consistency in the product. Later, similar data were submitted for Type 2 and Type 3 virus vaccines by the Bureau.

Other than data on the viral isolates from vaccine recipients mentioned above, there is no product-specific information regarding human safety. The Pfizer brochure mentions use of WI–38 cells to produce vaccines containing poliovirus; adenovirus Type 4; rhinovirus; and measles, rubella, smallpox, varicella, and arboviruses which, in the aggregate, have been given in the United States and Eurpoe to over 2 million persons with no reports of any untoward effects due to adventitious agents. No specific reference is made to poliovirus vaccines or to possible effects of vaccine strain polioviruses. The material on file in the Bureau of Biologics contains a fairly detailed summary of the experience of Ikic' in Yugoslavia with vaccines produced in WI–38 cells, and this was accepted as evidence of compliance with the requirement that the human cell line be "shown to be capable of producing a vaccine which, by experience in at least 10,000 persons, has been found to be safe and antigenic" (21 CFR § 630.12(b)).

c. *Benefit/risk.* The available evidence suggests that Diplovax does not differ in safety or efficacy from trivalent vaccine produced in MKC. The generic discussion should be consulted.

d. *labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions.*

a. *Critique.* A serious effort was made to study reversion rates in progeny virus descended from vaccine virus propagated in human diploid cells, but a concurrent parallel study of progeny derived from virus grown in MKC

unfortunately was not done. Such a study is urgently needed.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. The need for a stury on the reversion rate of vaccine virus grown in MKC has been noted. The potential superiority of established human strains, such as WI–38, as a long-lasting, single source of cells over primary cells obtained from animals is such that a special effort should be made to identify, and follow over an extended period, a sizeable group of recipients of Diplovax. This would gradually provide a more solid basis for judging the safety for man of vaccines so produced.

Poliovirus Vaccine, Live, Oral, Types 1, 2, and 3 (Sabin) Manufactured by Pfizer, Ltd.

Insufficient information was provided by the manufacturer for these monovalent products, which the company was licensed to manufacture at the time of this review. The manufacturer has never marketed the monovalent components of the currently licensed product in this country. In the absence of sufficient information from the manufacturer concerning labeling and marketing experience with the monovalent products, the Panel can make no determination regarding their relative benefits and risks, and the panel must recommend that these products be placed in Category IIIB and that the appropriate licenses be revoked.

Poliovirus Vaccine, Live, Oral, Trivalent (Sabin); and Poliovirus Vaccine, Live, Oral, Types 1, 2, and 3 (Sabin) Manufactured by Wyeth Laboratories, Inc.

This vaccine has not been manufactured for a number of years and the only way to assure that competence currently exists for its production, and to guarantee its safety and efficacy, is to require a new submission when or if Wyeth Laboratories, Inc., desires to resume marketing of the vaccine. It is recommended that 21 CFR 601.5 be invoked, whereby the Commissioner may recommend that a license be suspended or revoked upon finding that "manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made."

Furthermore, if the manufacturer proposes to resume production, the panel recommends that this product be placed in Category IIIB and that appropriate license(s) be revoked pending completion of additional testing and conformance with the recommendations of this report because there is no evidence presumptive of safety or effectiveness for this product.

References

(1) "Morbidity and Mortality Weekly Report," Center for Disease Control, Public Health Service, Department of Health, Education, and Welfare, Volume 26, No. 40, October 7, 1977.

(2) Gard, S., "Inactivation of Poliovirus by Formaldehyde. Theoretical and Practical Aspects," *Bulletin of the World Health Organization,* 17:979–989, 1957.

(3) Craig, D. E. and G. C. Brown, "The Relationship Between Poliomyelitis Antibody and Virus Excretion From the Pharynx and Anus of Orally Infected Monkeys," *American Journal of Hygiene,* 69:1–12, 1959.

(4) Bottinger, M., "Experiences from Investigations of Virus Isolations From Sewage Over a Two Year Period With Special Regard to Poliovirus," *Archiv fur die gesamte Virusforschung,* 41:80–85, 1973.

(5) Ashkenazi, A. E. and J. L. Melnick, "Poliomyelitis Antibody Levels of young Children in Houston, 1961–62. Existence of Susceptible Pockets in an Area Using Salk Vaccine of High Effectiveness," *Texas Reports on Biology and Medicine,* 20:550–554, 1963.

(6) Potash, L., H. M. Glefand, and J. P. Fox, "Studies on the Development of Natural Immunity to Poliomyelitis in Louisiana. VI. The Incidence of Poliovirus Infections During 1958 as an Indication of the Effect of Salk-type Vaccine on Virus Dissemination," *American Journal of Hygiene,* 71:418–426, 1960.

(7) Swartz, T. A., P. Skalska, C. G. Gerichter, and W. C. Cockburn, "Routine Administration of Oral Polio Vaccine in a Sub-tropical Area. Factors Possibly Influencing Sero-Conversion Rates," *Journal of Hygiene,* 70:419–426, 1972.

(8) Rasmussen, C. M., C. W. Thomas, R. J. Mulrooney, and R. A. Morrissey, "Inadequate Poliovirus Immunity Levels in Immunized Illinois Children," *American Journal of Diseases of Children,* 126:465–469, 1973.

(9) Francis, T., Jr., et al., "Evaluation of 1954 Poliomyelitis Vaccine Trails," *American Journal of Public Health,* 45(5), Part 2, 1–63, 1955.

(10) Hale, J. H., M. Doraisingham, K. Kanagaratnam, K. W. Leong, and E. S. Monteiro, "Large-scale Use of Sabin Type 2 Attenuated Poliovirus Vaccine in Singapore During A Type 1 Poliovirus Epidemic," *British Medical Journal,* 1:1541–1549, 1959.

(11) "Annual Poliomyelitis Summary 1971," *Neurotropic Diseases Surveillance,* Center for Disease Control, issued March 1973.

(12) "Annual Poliomyelitis Summary 1972," *Neurotropic Diseases Surveillance,* Center for Disease Control, issued October 1974.

(13) "Annual Poliomyelitis Summary 1973," *Neurotropic Diseases Surveillance,* Center for Disease Control, issued February 1975.

(14) Shah, K. and N. Nathanson, "Human Exposure to SV40; Review and Comments," *American Journal of Epidemiology,* 103:1–12, 1976.

(15) Sabin, A. M., "Commentary on Report on Oral Poliomyelitis Vaccines," *Journal of the American Medical Association,* 190:52–55, 1964.

(16) "Summary of Immunization Status for Polio, DTP, Measles, and Rubella," United States, Center for Disease Control, Public Health Service, Department of Health, Education, and Welfare, 1974.

Generic Review of Smallpox Vaccines

Background

To our knowledge, smallpox vaccines have not before been subjected to a thorough systematic review for safety and effectiveness. The basis for the standards used in their licensure in many cases are decades old. Because these vaccines present certain generic problems which can be addressed in a general way, the specific product reviews are introduced with this broad statement. Some of the general recommendations will appear at the end of this review; others will be outlined in the product reviews which follow.

It must be recognized that there are no other licensed vaccines which permit a measurable bacterial count in an injectable product. In addition, there are no other live viral vaccines where the passage history of the seed virus is unregulated and where a seed lot system of some sort is not uniformly in use. Furthermore, there are few other vaccines whose administration is associated with such a degree of morbidity. Nevertheless, smallpox vaccine is, generically speaking, of proven effectiveness. There is a problem, however, in proving the effectiveness of specific products which have never been used under field conditions in the control of an epidemic. This is not a purely academic consideration, since it seems quite possible that vaccine made from a strain of vaccinia virus distantly related to established strains might no longer protect against smallpox. A classic protection study of course, cannot be reasonably demanded from each company producing vaccine. Is protection against challenge with a standard strain of vaccinia virus an adequate substitute for such efficacy trials? Perhaps, but it should be noted that the studies of Wesley and other describe the capacity of the CV–1 strain to protect against challenge while at the same time apparently inducing only low or undetectable amounts of neutralizing antibody (Refs. 1 and 2).

For many years, routine smallpox immunization of all children in the United States was both the recommended and the accepted medical practice. As the World Health Organization (WHO) smallpox

eradication progressed, and as worldwide importation smallpox outbreaks decreased in frequency, it became increasingly evident that the morbidity of vaccinia virus inoculation outweighed the risk of exposure to smallpox itself. For this reason, in 1972 routine smallpox immunization was no longer considered advisable, and the recommendation of ACIP in that year (the latest available) reads as follows:

At the present time, the routine use of smallpox vaccine as part of pediatric immunization schedules is not recommended in the United States. Selective vaccination of persons at potential risk of contracting smallpox should be continued.

International travelers. All travelers going to endemic or infected areas should be vaccinated before departing from the United States. For purposes of validating an International Certificate of Vaccination, primary vaccinations must be inspected, and the traveler revaccinated if the initial vaccination were not successful. Although inspection of revaccination is not required by international regulations, health workers are strongly encouraged to examine the revaccination site and again revaccinate the traveler if a major reaction has not occurred (see General Vaccination Information).

High risk groups. Hospital and health personnel constitute the first line of defense after importation. The large percentage of secondary cases acquired in hospitals following importations in Europe warrants maintaining high level immunity in this group. A regular program of revaccination every 3 years is recommended for all hospital and medical personnel and public health and allied professions.

More recently, in an interim report ("Morbidity and Mortality Weekly Report," January 17, 1976) ACIP has withdrawn its recommendation for systematic programs of routine vaccination of hospital and health personnel.

In spite of these recommendations, smallpox vaccination is still widely practiced in this country. There are many physicians who disagree with the discontinuance of routine smallpox immunization and who vaccinate all children after their first birthday. Many adults are immunized for international travel, even though published requirements for entry into many countries no longer require it. Moreover, largely because of frustration with other therapeutic modalities, vaccination is widely performed for treatment of such common ailments as aphthous stomatitis, recurrent herpes labialis, and recurrent gential herpes, in spite of a conspicuous lack of evidence for its efficacy. It is hoped that, as the eradication of smallpox becomes a reality and with increasing education of physicians, these misguided practices will cease.

The ACIP enumerates the following contraindications to smallpox vaccination (1972):

Skin disorders. Eczema and other forms of chronic dermatitis in the individual to be vaccinated or in a household contact are contraindications to vaccination. An inquiry into the family history for skin disorders should always take place before vaccination. If vaccination is required for an individual with dermatitis because of potential exposure in an endemic or infected area, Vaccinia Immune Globulin (VIG) should be administered to the vaccinee at the time of vaccination. VIG will not prevent successful vaccination. If there is real need to vaccinate an individual who may thus create a hazard for a household contact with dermatitis, consideration should be given to separating the vaccinee from his contact until the vaccination lesion has healed.

Pregnancy. In rare instances, vaccinia virus crosses the placental barrier and infects the fetus. Of the few reported cases of fetal vaccinia, virtually all have followed primary vaccination. If vaccination is indicated because of possible exposure to smallpox, VIG should generally be given simultaneously with the vaccine, particularly in cases of primary vaccination.

Altered immune states. Leukemia, lymphoma, and other reticuloendothelial malignancies; dysgammaglobulinemia; therapy with immunosuppressive drugs, such as steroids and antimetabolites or radiation are strong contraindications to vaccination. Vaccination should be considered only under circumstances of actual smallpox exposure. If such a person is exposed to smallpox making vaccination mandatory, VIG should be given at the time of vaccination.

Analysis

1. *Efficacy.* Recommendations concerning effectiveness are based on the conviction that the protective effect of a smallpox vaccine is dependent on the strain of virus used, the infective titer of the product at the time of its use, and the mode of its administration. If these can be regulated, effectiveness will be assured in so far as possible.

2. *Safety.* Safety is to a large extent dependent on the strain of virus used, the mode of its administration, and the proper selection of recipients. Although immediate safety can be monitored for each product regardless of the strain of virus used in manufacture, possible long-term effects and rare events such as encephalitis may be difficult to control. Thus, for safety as well as efficacy, the virus strain appears to be important.

3. *Benefit/risk.* The benefit/risk ratio of smallpox vaccines varies with the circumstances of their use. In the United States the benefit probably exceeds risk only for travelers to endemic areas and for hospital and other personnel directly exposed to risk. This judgment is based on statistics of morbidity due to smallpox vaccination. The data are summarized in Table 9.

Table 9.—*Complications Associated With Smallpox Vaccination per 1 Million Vaccinations*

Complication	Complications per million primary vaccinations					Complications per million revaccinations—all ages
	Age at vaccination				All ages	
	<1	1 to 4	5 to 19	20+		
Death (from all complications)[1,2,3]	5.0	0.5	0.5	(6)	1.0	0.1
Postvaccinal encephalitis	6.5	2.2	2.6	3.5	2.9	.0
Vaccinia necrosum[2]	0.0	0.4	1.0	[illegible]	.9	.7
Eczema vaccinatum[4]	14	[illegible]	35	[illegible]	38	3
Generalized vaccinia[4]	394	233	140	212	242	9
Accidental infection[4]	507	577	371	[illegible]	529	42
Erythematous urticarial reactions[5]	(6)	(6)	(6)	(6)	(6)	(6)

[1] Neff, J. M., J. M. Lane, J. H. Pert, R. Moore, J. D. Millar, and D. A. Henderson, "Complications of Smallpox Vaccination: I. National Survey in the United States," *New England Journal of Medicine* 276:125-132, 1967.

[2] Lane, J. M., F. L. Ruben, J. M. Neff, and J. D. Millar, "Complications of Smallpox Vaccination, 1968: National Surveillance in the United States," *New England Journal of Medicine*, 281:1201-1208, 1969.

[3] Lane, J. M. and J. D. Millar, "Risk of Smallpox Vaccination Complications in the United States," *American Journal of Epidemiology* 93:238-240, 1971.

[4] Lane, J. M., F. L. Ruben, J. M. Neff, and J. D. Millar, "Complications of Smallpox Vaccination, 1968: Results of Ten Statewide Surveys," *Journal of Infectious Diseases*, 122:303-309, 1970.

[5] Neff, J. M. (unpublished data).

[6] Unknown.

Source: "Morbidity and Mortality Weekly Report," 9/25/71, CFC, PHS, DHEW

In 1968, there were at least 9 deaths due to vaccination (6 in primary vaccinees, 2 in revaccinees, and 1 in a contact), 16 cases of postvaccinia encephalitis (all in primary vaccinees), 11 of vaccinia necrosum (5 in primary vaccinees), 126 of ecxema vaccinatum (58 in primary vaccinees, 8 in revaccinees, and 60 in contacts), 143 of

generalized vaccinia, and 193 accidental infections. All of these figures are derived from reported cases. The true rates of the various complications of smallpox vaccination are unknown but are undoubted higher than this.

When there is danger of exposure to smallpox, the benefit-risk ratio rises. This important concept should be made clear to individuals using and receiving vaccine.

Recommendations

1. *Efficacy.* Because control of the strain of vaccinia virus in the vaccine appears to be the most feasible way of assuring efficacy, it is recommended that all manufacturers use the same strain and assure uniformity by use of a seed lot system. At the present time, only vaccine produced by certain manufacturers has been proven effective. The possibility should be explored that a primary seed lot produced by one of these manufacturers might be provided for use as seed for all licensed manufacturers. The regulation of the seed lot system can be based on the recommendations made in 1965 by WHO and incorporated in World Health Organization Technical Report Series, No. 323, Annex 4, Section 3.1, pp. 60–61, 1966.

2. *Potency.* Potency in vitro should be better defined. In this regard, we look on the rabbit scarification method as being inferior in its quantitative aspects to the pock counting method. It is recognized that a rabbit skin response possesses some physiologic meaning since it measures dermotropism as well as infective units, and in this and other respects it may be closer to a measurement of vaccine potency in man. However, control of vaccine strain and passage history should control these variables. Moreover, the use of the present "either/or" requirement does not seem logical if one system is clearly better than the other or if both are necessary. Therefore, in vitro potency should be defined by the pock counting method and, as at present, the vaccine lot in question should be compared with an FDA standard. The Panel notes with approval that the Commissioner published a proposed change to this effect in the **Federal Register** of March 14, 1975 (40 FR 11884), which was adopted November 19, 1976 (41 FR 51009) (21 CFR 630.70, 630.73, 630.74).

b. Each manufacturer should provide a clear statement of the product's potency in man. Each manufacturer should test initially, and in addition whenever there is a change in its manufacturing protocol, one lot of its vaccine in 50 primary vaccines, with a required take rate of greater than 95 percent.

3. *Sterility.* The Panel questions whether the present standards for sterility are adequate. It is recommended that the standards for percutaneous vaccine be raised to those for jet-gun vaccine (1 organism per 100 doses) and that the jet-gun vaccine be bacteriologically sterile.

4. *Extraneous organisms.* The question is raised as to whether in addition to bacteria, other types of extraneous organisms should be searched for in calf lymph vaccines. Because the potential presence of such organisms has not caused any proven problems, it seems appropriate that at this time the matter should be examined in research laboratories before any decisions are reached requiring such tests of the manufacturers. An effort should be made to examine smallpox vaccines for adventitious viral agents and particles, and to cultivate mycoplasmas from calf lymph before preservatives are added.

5. *Quality of vaccine.* The Bureau of Biologics should continue to examine records of each manufacturer to ascertain the consistency of quality in production of vaccine including any lots not submitted for release.

6. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP. Inclusion of the following specific information is emphasized:

a. Indications for vaccination, according to the latest recommendations of ACIP;

b. Contraindications and precautions for vaccination, according to the latest recommendations of ACIP;

c. Anticipated complications of vaccination, including all those mentioned by ACIP, with some information as to their expected frequency;

d. A dating of ACIP recommendations which are being quoted;

e. A statement that certain contraindications to vaccination may be only relative in the face of exposure to smallpox, and that in such cases vaccinia immune globulin should be used;

f. The strain of vaccinia virus used to make the vaccine;

g. The potency of the vaccine, in pock forming units per ml, as related to the United States Reference Smallpox Vaccine.

Review of Individual Smallpox Vaccine Products

Smallpox Vaccine in Three Formulations: Glycerinated Vaccine; Dried Vaccine; Dried Vaccine for Jet Injection Manufactured by Connaught Laboratories, Ltd.

1. *Description.* Complete details of the production and processing are supplied for each formulation which describe the origin of the virus (Bureau of Laboratories, Department of Health, New York City in 1927), its passage history (renewal approximately every two years, until 1967, by exclusive passage on calves), and seed-lot system in use since 1967, (no more than five passages removed from the primary seed lot). Also given are the details of production of secondary seed lots and final production lots on calves, including selection of calves, skin preparation, inoculation procedure, measures to minimize soiling of vaccination area, treatment of the vaccination area during the incubation period, and, finally, the harvesting of the pulp followed by necropsy to insure the calves were free of any pathological condition. From this point on processing of the pulp differs according to the final vaccine formulation desired. The following descriptions are quoted from the package inserts submitted to the Panel.

Smallpoc vaccine (glycerinated) "is a suspension of live vaccinia virus propagated on calf skin. The vaccine has been shown by appropriate test methods to contain not more than 200 nonpathogenic organisms per ml and it will retain its potency until the date stamped on the package, providing it is constantly kept at not above 0° C. The virus is quickly inactivated at room temperature."

Smallpox vaccine (dried) is prepared "from partly purified suspensions of vaccinia virus propagated on calf skin and shown by appropriate test methods to contain not more than 200 nonpathogenic organisms per cubic centimeter (cc). During the preparation of the vaccine small amounts of streptomycin and neomycin are added. When reconstituted with the diluent provided, the vaccine contains not more than 0.5 mcg streptomycin and 0.25 mcg neomycin per 0.01 cc (approximately 1 dose) as well as 0.3 percent phenol.

The dry powder dissolves without difficulty in the diluent which consists of 40 percent glycerin in McIlvaine buffer containing 0.2 percent phenol.

Smallpox vaccine (dried) for jet injection is prepared "from partly purified suspensions of vaccinia virus propagated on calf skin and shown by appropriate test methods to contain not

more than one organism per 100 doses. During the preparation of the vaccine small amounts of streptomycin and neomycin are added. When reconstituted with the diluent provide, the vaccine contains not more than 0.25 mcg streptomycin and 0.13 mcg neomycin per 0.1 cc (approximately 1 dose) as well as 0.3 percent phenol. The diluent contains 0.2 percent phenol."

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic reviews.

2. *Analysis.* Information concerning safety, bacterial contamination, potency, stability, and final identity is given in complete detail in sections II and IV of the corresponding separate partial submissions.

The glycerinated vaccine must contain at least 10^8 plague forming units (pfu) per ml of vaccinia virus and, after 18 hours incubation at 37° C, must retain at least 10^7 pfu. The vaccine must be innocuous for guinea pigs and mice, must contain no more than 200 viable nonpathogenic organisms per ml and must contain no pathogenic bacteria, as judged by inoculation into guinea pigs of positive cultures from the tests for viable bacteria. Identity of vaccinia virus is established by the agar gel immunodiffusion technique, using antivaccinia virus serum and normal rabbit serum. For the freeze-dried formulation, basically similar criteria must be met except that in the freeze-dried state there must be no more than 1 percent residual moisture and there must be no loss of potency during 30 days storage at 37° C. For the freeze-dried material intended for jet injection, the criteria for acceptance differ from those just described chiefly with respect to bacterial content. This must not exceed more than one non-pathogenic bacterium per 10 ml (100 doses) of reconstituted product.

a. *Efficacy.* Data concerning efficacy are provided in the form of detailed reports of clinical trials with material from each of the three formulations. The criteria for efficacy are the proportion of primary takes in previously unvaccinated individuals and major reactions in those undergoing revaccination. All three formulations performed satisfactorily.

b. *Safety.* Data concerning human safety are supplied in consolidated form for all three formulations. During 1960–1972, many millions of doses of vaccine were distributed. Review of the data submitted on complications attendant upon vaccination revealed no unusual rate for this product.

c. *Benefit-risk.* See generic review.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions.* a. *Critique.* This submission is well documented and fully adequate.

b. *Recommendations.* The Panel recommends that these products be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for these products.

Smallpox Vaccine, Avianized Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* The package insert states the following:

> Smallpox vaccine, avianized, Lederle, is a suspension of vaccinia virus obtained from infected portions of the chorioallantoic membranes of embryonated chicken eggs. It is used for active immunization against smallpox * * * Antibiotics added to the virus inoculum in the preparation of this product are present in the final product at concentrations per vaccination which do not exceed 0.27 mcgm of neomycin sulfate, 0.5 units of polymyxin B sulfate, and 0.03 mcgm of tetracycline. The vaccine is stabilized and preserved with approximately 45 percent sorbitol w/v. The product contains no more than 200 viable organisms per ml.

The history of the origin of the Lederle vacinia strain is throughly detailed in the supplement to the submission.

RIF-free flocks which "meet the requirements of U.S. Pullorum-clean standards" are used for the production of eggs.

Potency is measured in eggs, and an equivalence has been shown for the avianized vaccine of pfu to potency determined in rabbits by scarification.

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.*

a. *Efficacy.*

(1) *Animals.* Not pertinent.

(2) *Humans.* In their submitted material, and in information from the Bureau of Biologics there is adequate information to conclude that this vaccine produces takes in an acceptable proportion of both primary recipients and revaccinees. Actual protection against smallpox by egg-grown vaccines has been claimed by at least three groups quoted in a paper by Espmark, (Ref. 3). In addition, unpublished reports claim that egg-grown vaccines were largely responsible for the eradication of smallpox in Brazil. None of these reports refers specifically to the Lederle product.

More recently, the Lederle egg-grown vaccine has been compared to the Wyeth "Dryvax" in a detailed protocol involving primary vaccination, revaccination, and extensive serologic studies, which was coordinated by the Infectious Disease Branch of the National Institute of Allergy and Infectious Diseases. The results of this study support the conclusions that the avianized vaccine performed identically to the calf-lymph product, from the points of view of reactogenicity infectivity in human skin production of hemagglutination-inhibiting and neutralizing antibody and protection against subsequent challenge with a standard vaccination (Ref. 4). In this study, 143 children received the Lederle vaccine subcutaneously and none experienced necrotic local reactions.

b. *Safety.* (1) *Animals.* The required tests for sterility and animal safety are performed. As mentioned above, RIF-free eggs are used. It is of interest that in spite of claims of the manufacturer (which, it must be said, do not appear in the package insert or in advertising), that the egg product is bacteriologically safer than calf-lymph vaccine; 47 percent of the chorioallantoic membrane (CAM) pools were contaminated, in some instances exceeding the allowable standards. Sorbitol has a bactericidal effect.

(2) *Humans.* Reported complications for 1968–1973 are enumerated, but are marketing data are not, so a denominator is not available. The company does not report an excess of adverse reactions with percutaneous vaccine. An unpublished manuscript was brought to the attention of the Panel (Ref. 5). According to this report, about 15 percent of recipients of egg-grown (Lederle-produced) vaccine developed deep necrotizing reactions when jet injector vaccine was used. These findings were discussed by the manufacturer at a meeting, and no satisfactory explanation for the reactions emerged. The company has never marketed jet injector vaccine.

c. *Benefit/risk.* See generic review.

d. *Labeling.* Labeling should conform to the FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions.* a. *Critique.* The avianized vaccine is in many ways a product preferable to the calf-lymph vaccine. Specialized facilities are not needed for its production, bacteriologically sterile vaccine i_s

resonable possibility, and production is efficient and inexpensive.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Additional analysis of the experience in India and Brazil with avianized vaccines, with special reference to effectiveness, should be done. In addition, the possibility of variable dermal toxicity among lots should be monitored because of the importance of this product and others like it in the future of smallpox vaccines.

Smallpox Vaccines Manufactured by Massachusetts Public Health Biologic Laboratories

No data have been provided by the manufacturer for Smallpox Vaccine for which they were licensed at the time this review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIB and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Smallpox Vaccine Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

This submission deals with a discontinued product. The submission and other available information fail to provide sufficient evidence to justify continued licensing. The license, therefore, should be revoked. It is recommended that § 601.5 be invoked whereby the Commissioner may recommend that a license may be suspended or revoked upon finding that "manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made." Furthermore, if the manufacturer proposes to resume production, the Panel recommends that this product be placed in Category IIIB and that appropriate license(s) be revoked pending completion of additional testing and conformance with the recommendations of this report because there is no evidence presumptive of safety or effectiveness for this product.

The Panel believes that the Bureau of Biologics interpretation of the regulations concerning permissible combinations (21 CFR 610.17) of licensed products to mean that a manufacturer must hold a license for smallpox vaccine in order to purchase and market another producer's licensed smallpox vaccine for a combined product should be modified, and if necessary, the regulation should be changed to allow an exception to be approved in this and perhaps other related instances.

Smallpox Vaccine and Smallpox Vaccine Freeze-Dried Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* Liquid vaccine is stated to be a glycerinated live virus vaccine, prepared from calf lymph * * *. The vaccine has been shown by appopriate test methods to contain not more than 200 organisms per ml. For color contrast, brilliant green (1:6,000) has been added. Preservative: 0.4 percent phenol. [The freeze-dried vaccine] contains a purified suspension of the live virus of vaccinia (cowpox) and is derived directly from calf lymph. The vaccine has been shown by appropriate test methods to contain not more than 200 organisms per ml. The purified virus, prior to freeze-drying, is suspended in an aqueous solution of sodium chloride (0.85 percent), 1:10,000 benzalkonium chloride, 1:6,000 brilliant green for color contrast and stabilized with peptone (5 percent). The diluent for the reconstruction of Smallpox Vaccine, Freeze-Dried consists of glycerin 50 percent in sterile distilled water. The preservative is phenol (0.25 percent).

Potency in vitro is measured in pock-forming units in relation to FDA standards and is acceptable (data supplied on five lots).

The manufacturing process is adequately described; although care of the calves and harvest of lymph are not outlined in the submission, subsequent treatment of the vaccine is detailed.

a. *Recommended use.* See the generic discussion.

b. *Contraindications.* See the generic discussion.

2. *Analysis.* a. *Efficacy.* (1) *Animals.* Not pertinent.

(2) *Humans.* Data are submitted for trials in 1961 when 19 primary vaccinees (out of 19) had takes, and the considerable data on revaccinees indicate a potent vaccine.

b. *Safety.* (1) *Animals.* The product satisfies the FDA regulations in regard to sterility and animal safety.

(2) *Humans.* The information presented is based on the marketing experience from 1968 through 1972 and includes many millions of doses of both liquid and freeze-dried vaccine. Review of the data submitted on complications revealed no unusual rate for this product.

c. *Benefit-risk.* See generic review.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions.* a. *Critique.* See the generic product review.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Smallpox Vaccine Manufactured by Division of Biologic Products Bureau of Laboratories, Michigan Department of Public Health

1. *Description.* The vaccine consists of a 50 percent suspension in glycerol with 0.5 percent phenol of liquid vesicular material from healthy calves vaccinated with vaccinia virus. This suspension is put up in capillary tubes, five per package, together with scarifying needles and rubber bulbs.

The virus strain employed is derived from strain #999 obtained in 1937 from the Massaschusetts Antitoxin and Vaccine Laboratory (the origin of strain #999 is not known). Since then, it has been given annual cycles of rabbit-calf passage, with each calf passage providing the seed for one season.

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.* a. *Efficacy.* Prior submissions, together with supplementary ones, report on tests of activity of smallpox vaccine conducted from 1948 through 1972. The results are summarized in Table 10.

Table 10.—*Results of Potency Tests, Smallpox Vaccine, Michigan Department of Public Health*

Year	Results of vaccination (takes/recipients)	
	Primary vaccination	Revaccination
1948	2/2	6/7 (1 [1])
1950	6/6	17/38 (21 [1])
1958	5/5	5/10 (5 [1])
1963		
1965	9/9	
1970-72	24/26	21/35

[1] Classed "immune."

Such tests are conducted periodically. The results suggest potency for man is basically adequate for primary vaccination. The record for revaccination, 49/90 or 55 percent, is less reassuring but may reflect a combination of poor vaccination technique, the inclusion of many recently vaccinated persons, and failure to use WHO criteria for classification of response.

b. *Safety.* (1) *Animals.* The submission cites the standard tests in animals and the potency test in rabbits.

(2) *Humans.* Data are provided on millions of doses distributed between 1961–72. A review of the data submitted on complications revealed no unusual rate for this product.

c. *Benefit/risk.* See generic review.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions.* a. *Critique.* See generic review.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Smallpox Vaccine ("Dryvax") Manufactured by Wyeth Laboratories, Inc.

1. *Description.* This is a lyophilized preparation of calf lymph containing vaccinia virus. The vaccine is reconstituted with 50 percent glycerine for inoculation by the multiple pressure technique or with .02M phosphate buffered saline for administration by jet gun. The reconstituted vaccine contains no more than 200 organisms per cc and the upper limits of the antibiotics employed during processing are stated as being not more than 100 u/cc polymyxin, 200 mcg/cc dihydrostreptomycin, 200 mcg/cc chlortetracycline, and 100 mcg/cc neomycin.

Vaccine comes with or without brilliant green, and in a form intended for jet-gun use only or in one not intended for jet-gun use.

Potency is measured *in ovo* by pockforming units and is adequate and well defined for two lots.

The production method is well described in material provided by the Bureau of Biologics from its license files.

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.* a. *Efficacy.*

(1) *Animals.* Not pertinent.

(2) *Humans.* The recording of take rates (both primary and revacination) is adequate. Wyeth Laboratories, Inc., in addition, submitted the following statement:

> Wyeth was the principal supplier of vaccine to a major phase of the eradication program carried out in West and Central Africa in addition to its contributions to other parts of the global program.

b. *Safety.* (1) *Animals.* The Bureau of Biologics' requirments for sterility and animal safety are satisfied.

(2) *Humans.* Minor complications of vaccination are well detailed in the data for Wyeth's product. However, the manufacturer does not submit either marketing data or data on major complications reported to them.

c. *Benefit-risk.* See generic review.

d. *Labeling.* Labeling should conform to the FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federl Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions.* a. *Critique.* See generic review.

b. *Recommentations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

References

(1) Wesley, R. B., W. C. Speers, J. M. Neff, F. L. Ruben, and B. Lourie, "Evaluation of Two Kinds of Smallpox Vaccine: CVI–78 and Calf Lymph Vaccine. I. Clinical and Serologic Response to Primary Vaccination," *Pediatric Research,* 9:624–628, 1975.

(2) Speers, W. C., R. B. Wesley, J. M. Neff, J. Goldstein, and B. Lourie, "Evaluation of Two Kinds of Smallpox Vaccine: CVI–78 and Calf Lymph Vaccine. II. Clinical and Serologic Observations of Response to Revaccination with Calf Lymph Vaccine," *Pediatric Research,* 9:628–632, 1975.

(3) Espmark, J. A., "Smallpox Vaccines: Attributes of Egg and Calf Lymph Vaccines," *First International Conference on Vaccines Against Viral and Rickettsial Diseases of Man,* Pan American Health Organization, Scientific Publication No. 147:466–474, 1967.

(4) Galasso, G. J., M. J. Mattheis, D. W. Alling, J. D. Cherry, A. Bairan, F. DeCastro, F. L. Horvath, U. T. Rolfe, J. D. Connor, J. E. Schanberger, A. S. Benenson, K. McIntosh, W. A. Todd, J. Nakano, and R. J. Romanoff, "Clinical Evaluation of Four Smallpox Vaccines," *International Symposium on Smallpox Vaccine, Symposia Series in Immunobiological Standardization,* 19:167–177, 1973.

(5) Vastine, D. W., L. H. Ratner, J. C. Bunn, J. M. Lane, and C. Nater, "Severe Necrotizing Vaccination Response to Jet Injector Inoculation of Vaccinia Virus Of Egg Origin," Center for Disease Control, Public Health Organization, Department of Health, Education, and Welfare, unpublished manuscript.

Generic Review of Measles Virus Vaccine

Background

Live measles virus vaccine falls into two generic categories: (1) attenuated Edmonston strain, and (2) further attenuated strains derived from the Edmonston strain.

About 4 million cases of measles, almost as many as the number of births each year, occurred annually in the United States before the development and widespread utilization of live attenuated measles vaccines. There were about 450 measles-associated deaths per year. The most frequent severe complications of measles were pneumonia and acute encephalitis; the latter occurred in 1 per 1,000 cases of natural measles infection (Ref. 1). In addition to this acute neurologic complication of measles infection, a much less common chronic form of encephalitis, which is fatal, occurs in approximately 0.5–1.0 case per 100,000 cases of measles infection. This chronic encephalitis associated with measles infection is called subacute sclerosing panencephalitis (SSPE).

In the late 1950's, John F. Enders and Samuel L. Katz initiated development of a live attenuated vaccine using the Edmonston strain of measles virus. This virus was repeatedly subpassaged in a variety of laboratory hosts. Each of the currently licensed vaccines was originally derived from one of two virus passage levels designated as the Enders A and the Enders B level, respectively. The passage history is shown in Table 11.

Table II.—*Derivation of the Enders A and Enders B Lines From the Edmonston Strain of Measles Virus*

Viral substrate	Number of serial passages
Primary human embryonic kidney (HEK)	24
Primary human amnion (HA)	28
Embryonated egg (E)	6
Chick embryo cell culture (CETC)	[1]13–A
Embryonated egg (E)	6
Chick embryo cell culture (CETC)	[1]3–B

[1] Level.

Thus a pool of virus (designated as 373C) at the A passage level was HEK–24 HA–28 E–6 CETC–13. The B passage level pool (designated as 749D) was HEK–24 HA–28 E–6 CETC–13 E–6 CETC–3.

The first vaccine was licensed in 1963 and by 1965 several other manufacturers received licenses. These vaccines were commonly administered in conjunction with Measles Immune Globulin (Human) in order to decrease the rates of reactivity (febrile response and rash) seen following vaccination. In 1965 and 1968, vaccines prepared from derivatives of the Edmonston virus obtained after additional serial laboratory passage were licensed. These vaccines were less reactogenic for man and could be administered without the concomitant use of globulin. Such preparations are currently the most commonly used.

Following the widespread use of measles vaccine, there has also been a

dramatic decrease in the number of measles associated deaths. This is due in large part to the high protective effect of the vaccine, the elimination of complications such as pneumonia, and the low incidence of acute neurologic disorders following administration of measles vaccine; the latter incidence is not very different from the "background" rate of encephalitis in young children (approximately one case per 1 million children as compared to a rate of one case of acute encephalitis per 1,000 children following natural measles infection). The earliest live attenuated measles vaccines had an incidence rate of associated extensive neurologic disorders of 1.61 per 1 million doses of measles vaccine, and the further attenuated vaccines subsequently developed have a lower incidence rate of 0.78 cases of acute encephalitis per 1 million doses of vaccine. Thus, the use of measles virus vaccines has led to a marked decrease in acute encephalitis due to measles infection.

However, the effect of measles vaccines on the incidence of the chronic type of encephalitis (SSPE) associated with measles virus infection is more difficult to discern. There are two major reasons for this: (1) The incidence of SSPE prior to the introduction of measles vaccine is not well defined. Several names were applied to the clinical syndrome and their identification as a single illness was not made until the association of measles with this disorder was confirmed in the late 1960's. In the absence of intensive prospective and retrospective studies, therefore, it was difficult to determine the incidence of SSPE until the early 1970's. (2) Although the interval between infection with measles virus and the expression of the clinical disease is variable, it is usually quite long, averaging 7 years.

Recently, more complete information has been obtained by the Bureau of Biologics, the Center for Disease Control, and scientists at the University of Tennessee relative to the epidemiology of SSPE during the past 8 years (Ref. 2). Some important epidemiologic findings have been made. The annual incidence of this rare but fatal disease has been decreasing the past few years in the United States (approximately 45 cases of SSPE occurred annually between 1966–1971, but in 1975 and 1976 there were 12 and 10 new cases, respectively, in the United States). The following findings were observed in patients with SSPE who had a history of measles immunization: (1) there was no relationship between onset of SSPE and age at time of vaccination; (2) SSPE occurred a mean of 3.3 years after vaccination, and (3) the potential risk was 0.48–1.13 cases of SSPE per million estimated measles vaccine recipients.

A recent update of this carefully case-controlled study (published in "Morbidity and Mortality Weekly Report," September 23, 1977) reported as follows:

> Fifty-two children with SSPE diagnosed since January 1, 1974, were each matched by age, sex, and race with both a long-term playmate and a hospitalized child. Vaccination and disease histories, verified by medical records review, were available for all cases and for 96 controls (Table 1). Children with SSPE were significantly more likely to have had natural measles than were controls ($p > .001$). Control children were significantly more likely to have received measles vaccine than were SSPE cases ($p > .001$). There was no difference between cases and controls with regard to having received measles vaccine after having had natural measles (21.2% vs 20.8%).

Table 1.—*History of Measles Infection and Measles Vaccination in 52 Children With SSPE and 96 Control Children*

Measles disease/vaccine history	SSPE cases (percent)	Controls (percent)
Had natural measles; no measles vaccination	32 (61.5)	25 (26)
Had natural measles; received measles vaccine	11 (21.2)	20 (20.8)
Had no history of measles; received measles vaccine	6 (11.5)	43 (44.8)
Had no history of measles or measles vaccination	3 (5.8)	8 (8.3)
Total	52	96

Two SSPE cases (3.8%) and 4 control children (4.2%) had received 2 or more doses of measles vaccine. Eleven SSPE cases (21.2%) had natural measles before they were 1 year old compared to 4 control children (4.2%) ($p > .01$). Four control children but none of the SSPE cases had received measles vaccine before they were 1 year old.

In short, it appears that utilization of measles vaccine has been associated with no detectable increase in the number of new cases of SSPE in the United States. In fact, the data currently available suggest that if there is any risk of developing SSPE following measles vaccination, it would be less than that associated with the alternative, i.e., natural infection with the virus. Obviously, more data are needed concerning these relationships (Ref. 3).

The Public Health Service Advisory Committee on Immunization Practices generally recommends that all susceptible children, i.e., those who have not had measles or measles vaccine, should be vaccinated after 1 year of age (15 months) with a single dose of live measles virus vaccine (Refs. 4 and 5). If an Edmonston B strain vaccine is to be used, it is recommended that it be accompanied by measles immune globulin, 0.01 ml/lb of body weight, given with different syringes at different sites. Measles immune globulin should *not* be given with further attenuated measles vaccines.

In the face of an epidemic or in areas with high measles incidence in the first 15 months of life, it may be desirable to vaccinate infants as young as 6 months of age, in which case these children should be revaccinated after reaching 15 months of age.

It is further recommended that children vaccinated before the age of 13 months, particularly if measles immune globulin was given concomitantly, be revaccinated. Also children who received killed measles vaccine should be vaccinated with live vaccine. High risk groups in which immunization is particularly important include children with chronic illnesses such as heart disease, cystic fibrosis, and tuberculosis, and those who are malnourished or institutionalized.

It is noted that live measles vaccine can usually prevent disease if administered within 2 days of exposure. It is rarely necessary to immunize adults, but no special untoward effects have been noted when this is done.

Precautions listed include: severe febrile illness, tuberculosis not under active treatment, recent administration of immune serum globulin (within 3 months), or marked hypersensitivity to vaccine components (chicken protein, etc.).

Contraindications listed include: altered immune states (leukemia, lymphoma, generalized malignancy, chemical immunosuppression, radiation therapy) and pregnancy.

The Food and Drug regulations governing manufacture of live, attenuated measles virus vaccines include specification of a seed lot system, with appropriate testing of new seed lots for neurovirulence. Chick embryo tissue must be derived from flocks certified to be free of obvious fowl pathogens and of avian leucosis, Rous sarcoma and "other adventitious agents pathogenic for chickens" (21 CFR 630.32(b)).

Virus in the final vaccine must be no more than ten tissue culture passages beyond the passage used to perform the clinical trials which qualified the manufacturer for license of that strain. Only primary cell cultures shall be used in the manufacture of Measles Virus Vaccine, Live, Attenuated.

Additional testing for safety includes mouse inoculation (21 days' observation of adult mice, 14 days' observations of

suckling mice), inoculation of embryonated chicken eggs, and inoculation of monkey, chick, and human cell cultures. Bacteriologic and complement-fixation for avian leucosis virus (COFAL) testing are done.

The potency required is "no less than the equivalent of 1,000 $TCID_{50}$ of the U.S. reference per human dose" (21 CFR 630.34).

Labeling requirements include specification of dose and a statement of caution about inactivation by temperature and light.

Analysis

1. *Efficacy.* Experience in the use of live, attenuated measles vaccines now covers more than 12 years and some 80 million doses. In terms of seroconversion, all preparations result in at least 95 percent responses in susceptibles over the age of 13 months. In addition, in epidemic situations the protective efficacy has ranged from 83 to 98 percent. Groups of apparent vaccine failures include:

a. Those who received killed measles vaccine or followed shortly thereafter by live vaccine when it was available before 1968;

b. Those who received live attenuated measles virus vaccine, Edmonston B strain, with or without human immune serum globulin (ISG) before 13 months of age;

c. Those who received further attenuated measles virus vaccine with ISG in a dose intended for use with the more reactive Edmonston B vaccine;

d. Those who received live measles vaccine that had lost its potency because of exposure to excessive light or heat.

Duration of protection has been well evaluated in several studies. Adequate levels of antibody have been demonstrated 11 years postimmunization in nearly all vaccines with no exposure over the intervening years; thus, there is no evidence at present to suggest the need for reimmunization in general.

2. *Safety.* Both the Edmonston B and further attenuated vaccine strains have been shown to be remarkably safe in terms of major complications. In fact, the incidence of neurologic illness occurring within 4 weeks of measles vaccination is as low as, if not lower than, that in the general population, i.e., 2 per million per 4 week interval. In only one instance has isolation of a measles vaccine-like virus actually substantiated a possible association of vaccination and neurologic disease. It is noteworthy that the risk per million in the past few years has been substantially lower than in the first years of immunization with attenuated virus, which suggests that the further attenuated strains in current use may be even safer than the Edmonston B type of attenuated virus vaccine. However, this is a minor point since at no time has clear proof been addressed to indicate the vaccine as etiologically responsible for neurologic disease at or above background levels.

In terms of minor complications, the Edmonston B type vaccine must be distinguished from further attenuated strains. The former evokes a modified measles rash in 30 to 60 percent of instances, and significant percentages of recipients experience fever of 103° F or greater lasting 2 to 5 days. While these manifestations are usually not accompanied by toxicity or significant disability, they are sufficiently prominent to result in the recommendation that gamma globulin be given simultaneously. This additional procedure introduces an entirely new set of risks (e.g., second injection; dosage error resulting in failure of vaccine take, etc.). This makes this class of measles vaccine less useful in the overall balance than the further attenuated vaccines. These latter preparations evoke only mild manifestations (low grade fever and/or rash in up to 20 percent of recipients) and at a level insufficient to necessitate gamma globulin administration.

3. *Benefit/risk.* All of the above considerations result in an excellent benefit/risk ratio. The benefit of widespread, early vaccination of susceptibles against measles is clear: the prevention of approximately 95 percent of instances of measles, with a durable protective immunity. Unmodified measles is associated with a risk of numerous respiratory complications and about one instance of overt encephalitis per 1,000 cases of measles, at least 400 deaths per year, and unmeasured additional instances of minimal neurologic damage. The risk of the vaccine is, at most 2 per million doses distributed in terms of major neurologic disease, so that the benefit to risk ratio is enormously in favor of live attenuated measles virus immunization. (see Fig. 3.)

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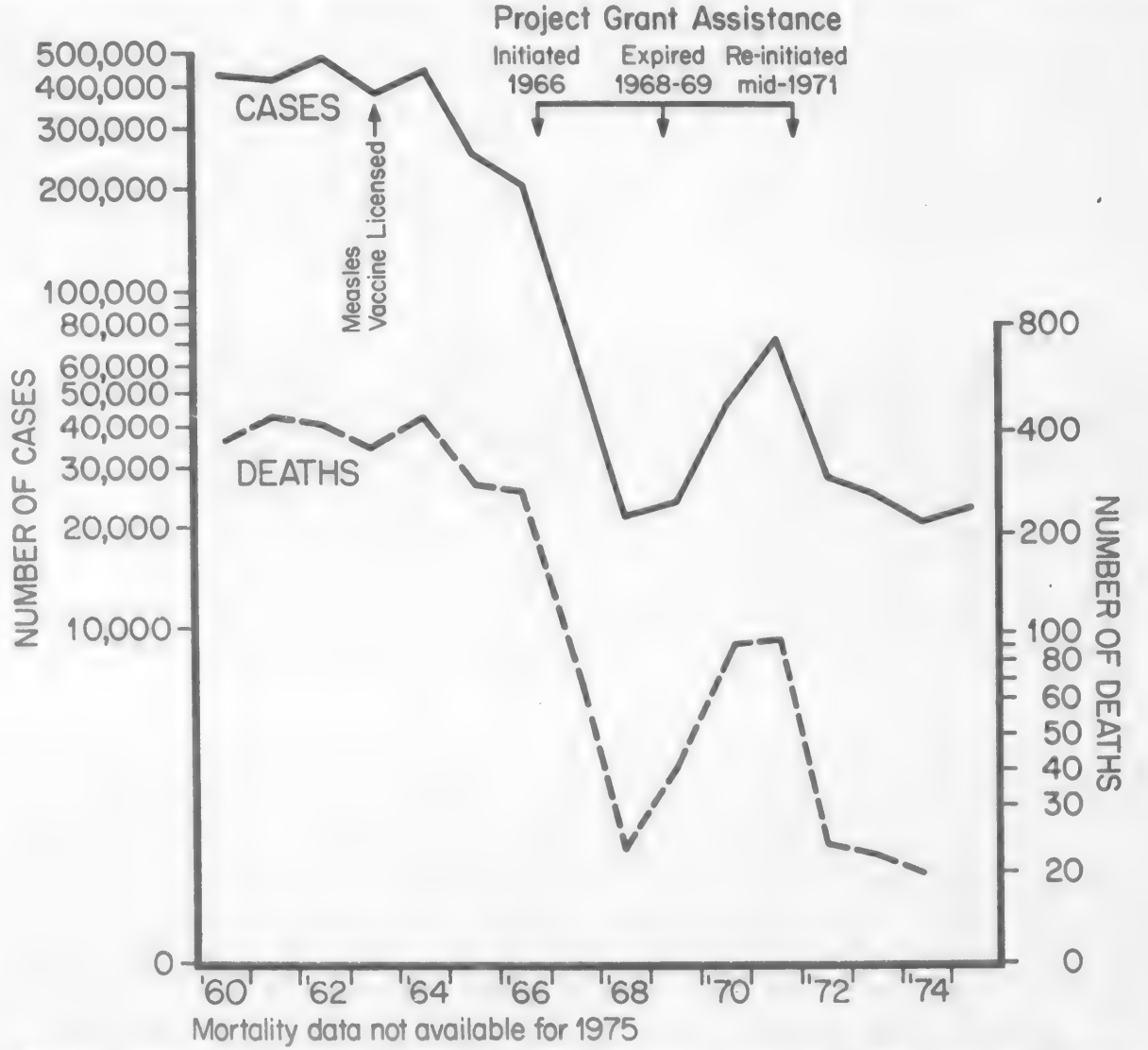
Figure 3

Reported Measles Cases and Deaths, United States - 1960-1975



Source: Center for Disease Control, Bureau of State Services, Immunization Division

The Edmonston strain clearly has a greater risk of minor complications and gamma globulin adds additional risk factors. Both of these points thus weigh in favor of the currently employed further attenuated measles vaccine preparation.

The issue of SSPE has been raised as an additional possible risk of measles vaccination, as it is of measles itself. However, more than 10 years have passed since widespread vaccination was initiated, and the incidence of SSPE has decreased as vaccination has continued.

4. *Labeling. Labeling should conform to the FDA's proposed regulations for labeling for prescription drugs used in man as reported in the* **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

Recommendations

Further attenuated measles virus vaccines are excellent, safe preparations and licensure is appropriate and should be continued. The Edmonston B vaccine is notably more reactogenic and the need for it is questionable in view of the availability of superior products. Consideration might be given to continuance of the license for Edmonston B vaccine with the understanding that the manufacturer will take steps to develop a product that will be at or below the level of reactogenicity of other vaccines currently available.

Review of Individual Measles Virus Vaccine Products

Measles Virus Vaccine, Live, Attenuated (Schwarz Strain) ("Lirugen") Manufactured by Dow Chemical Co.

1. *Description.* The package circular states that it is * * * a highly attenuated measles (rubeola) virus vaccine that is usually well tolerated but still highly antigenic. Further attenuation of the Edmonston strain of virus decreases systemic reactions so that the simultaneous use of gamma globulin with LIRUGEN is not generally indicated.

The virus is propogated in chick embryo tissue culture using medium '199'. A residual of not more than 50 micrograms each of neomycin B sulfate and stretomycin and 0.000001 micrograms of amphotericin B are present per dose * * *.

Each single dose of LIRUGEN contains no less than 1,000 $TCID_{50}$ of measles virus expressed in terms of the assigned titer of NIH reference measles virus.

a. *Recommended use.* * * * for active immunication of children against measles (rubeola). It will not immunize against German measles (rubella). The vaccine should be administered to measles-susceptible children at 12 months of age or as soon thereafter as possible to provide protection in early life. * * * may be given as early as 9 months, repeating the injection at 12–14 months of age to assure an immune repsonse.

The vaccine is particularly recommended for children in institutionalized settings, with chronic diseases (e.g., cystic fibrosis, heart disease, and asthma and other chronic pulmonary diseases) and with tuberculosis under treatment.

The vaccine is not recommended for adults unless they reside in isolated areas and/or communities in which measles is not endemic.

b. *Contraindications.* These are given as marked sensitivity to chicken protein, eggs, feathers, generalized and/or hematologic malignancies, and acute respiratory disease or other active febrile infection. The vaccine should not be used in pregnant women and patients undergoing treatment with corticosteroids, irradiation, alkylating drugs, or antimetabolites.

2. *Analysis.*—a. *Efficacy.*

(1) *Animals.* The data are limited. This is of minor relevance in view of the human data.

(2) *Humans.* There is an enormous literature concerning the excellent efficacy of live, attenuated measles vaccine; much of the recent information concerns this particular strain (Schwarz). In summary, seroconversion occurs in over 95 percent of susceptibles over the age of 1 and antibody persists with or without asymptomatic reexposure, although it is relatively low for at least 10 years. In several epidemics where this vaccine has presumably or definitely been used previously in part of the exposed population, the protective efficacy has ranged from 91 to 98 percent. In general, vaccine failure has appeared to leave the individual completely susceptible, although there is some suggestion that a few previously vaccinated individuals had modified disease following natural exposure.

b. *Safety.*—(1) *Animals.* The routine tests have been done as required by regulations and no evident problem has been encountered.

(2) *Humans.* A febrile and/or exanthematous reaction occurs in approximately 20 percent of children. Precautions in giving the vaccine to children known to have febrile convulsions, cerebral injury, etc., are well delineated. The major risk is neurologic. Data concerning the occurrence of significant neurologic disease within 4 weeks of administering any live measles vaccine assign a risk of less than 2 per million doses, which is slightly lower than the random risk. In only one instance, a measles vaccine-like virus has been isolated, which serves to support a possible association of vaccination and disease. All other evidence has been serologic and/or circumstantial. It is noteworthy that the risk per million in the past few years has been substantially lower than in the first years of immunization with attenuated measles virus, suggesting that this and other further attenuated strains may be even safer.

c. *Benefit/risk.* The annual number of measles cases prior to introduction of the vaccine approximated the number of births per year—probably about 4 million. Of these, about 10 percent were reported. About 400 annual deaths from measles were reported; 750 annual cases of nonlethal, permanent neurologic damage were reported; other less striking residua, although not measurable, were quite possibly even more significant. National vaccination programs reduced this rate of reported cases to about 20,000; with temporary cessation of the program, the rate climbed to 75,000; and with renewed stress on immunization in 1971, it has again dropped. Thus, the benefit is at least 90 percent reduction in cases of measles, and a concomitant reduction in complications. When contraindications are observed, the risk is minimal, i.e., about two cases of neurologic disease per 2 million doses of vaccine. Thus, the benefit/risk ratio is enormously in favor of live, attenuated measles virus vaccine immunization, and sufficient data exist to state that this pertains specifically to the Schwarz strain.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and the updated recommendations of ACIP.

There is a potentially serious inconsistency in that the statement to protect the vaccine from light appears on the box but not on the vial.

The package inserts are good in most respects. There is a commendably emphasized note concerning potential confusion of rubeola with rubella.

3. *Conclusions.*—a. *Critique.* This submission is extensively supported by an accompanying literature, both published and preprinted.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Measles Virus Vaccine, Live, Attenuated (M–VAC) Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* The package circular states that M–VAC Measles Virus Vaccine, Live, Attenuated, Lederle, is a suspension of Edmonston strain measles virus, live, attenuated, propagated in chicken embryo cell culture. The virus suspension is stabilized with a protein (casein) hydrolysate and sorbitol, and then lyophilized. Each single dose vial contains not less than 1,000 $TCID_{50}$ of measles virus expressed in terms of the assigned titer of the Bureau of Biologics reference measles virus. A dose contains about 50 micrograms each of streptomycin and neomycin.

a. *Recommended use.* "* * * for immunization of all susceptible children against measles (rubeola)." The product is especially recommended for children with malnutrition, chronic illness (heart disease, cystic fibrosis, chronic pulmonary diseases), and those in institutional settings. For maximum efficacy, the vaccine "should be administered when children are at least 12 months old. When used * * * between 6 to 9 and before 12 months of age, there occurs some reduction in efficacy and repeat immunization (booster) after 1 year of age is recommended."

The live virus vaccine is recommended for all children who received inactivated measles virus vaccine. "The vaccine is not effective in the prevention of rubella (German measles)."

b. *Contraindications.* These are given as pregnancy; leukemia, lymphoma, and other generalized malignancies; during or following therapy which depresses cell-mediated immunity or resistance to disease such as steroids, irradiation, alkylating agents, and antimetabolites; severe febrile illness; active tuberculosis unless under active treatment; and known or suspected hypersensitivity to chicken egg protein. There is an added, excellent statement that if immediate protection against measles is required and vaccine is contraindicated, passive immunization should be considered and the dosage of gamma globulin is given.

2. *Analysis.*—a. *Efficacy.*

(1) *Animals.* The data are of minor relevance in view of data on man.

(2) *Humans.* The present product has the properties of Edmonston strain; 95 percent or more of susceptibles convert serologically; immunizing efficacy has been shown in community and institutional settings; and durable immunity persisting for at least 10 years has been demonstrated with or without asymptomatic reexposure. Antibody titers achieved after immunization of susceptibles with Edmonston strain attenuated measles virus have been found to be higher than those induced by further attenuated strains, but in both instances antibody persistence is of long duration.

b. *Safety.*—(1) *Animals.* The data given are appropriate, but they are not as germane as those dealing with experience in man.

(2) *Humans.* Minor complications, viz., fever and rash, are a frequent concomitant of this product; even when gamma globulin is given simultaneously, the incidence of fever over 103° F appears to be about 15 percent. Major complications have not been conclusively demonstrated, even though many millions of doses of Edmonston strain measles vaccine have been administered.

c. *Benefit/risk.* See generic review. The Edmonston strain clearly has a greater risk of minor complications (high fever, rash), and, since gamma globulin is recommended for simultaneous administration, several additional factors must be considered beyond those pertinent to the further attenuated measles vaccines. In favor of the Edmonston strain is its greater immunogenicity, as indicated by higher titers of HI antibody. However, there is no evidence of greater persistence of the antibody response elicited.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP. In addition, the label should state that the high incidence of febrile reactions can be decreased by a simultaneous inoculation of measles immune globulin.

3. *Conclusions.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. While this product is effective and safe with respect to major complications, it is more frequently associated with minor complications than are the more attenuated measles vaccines, and it is recommended in conjunction with gamma globulin whereas the others can be given alone.

Measles Virus Vaccine, Live, Attenuated, MSD (Attenuvax) Manufactured by Merck & Dohme, Division of Merck Sharp & Co., Inc.

1. *Description.* The package circular states that Attenuvax (measles virus vaccine, live attenuated, MSD) is a measles virus vaccine prepared by using a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain. The further modification of the virus in ATTENUVAX was achieved in the Merck Institute for Therapeutic Research by multiple passage of Edmonston virus in cell cultures of chick embryo at low temperature. Clinical studies have demonstrated that ATTENUVAX is highly immunogenic and well tolerated. The coadminstration of human immune globulin has not been necessary for reduction of clinical reactions. A single injection of the vaccine has induced a measles antibody response in 97 percent or more of susceptible persons.

a. *Recommended use.* The preparation is intened for active immunization of children 1 year of age or older against measles (rubeola). In high risk situations, the vaccine may be given as early as 9 months of age. It is especially recommended for children in institutions, those with inactive tuberculosis or tuberculosis under treatment, or with chronic disease (e.g., cystic fibrosis, heart disease, asthma or other chronic pulmonary disease). It is recommended for adults only if their isolated circumstances warrant, e.g., residence in nonendemic areas.

b. *Contraindications.*.These are given as sensitivity to eggs, chickens, chicken feathers, or neomycin; febrile illness; active untreated tuberculosis; leukemia, lymphoma, or other generalized malignancies; patients undergoing therapy with corticosteroids, irradiation, ACTH, alkylating agents, antimetabolities, gamma globulin deficiency (i.e., agammaglobulinemia, hypogammaglobulinemia, or dysgammaglobulinemia); and pregnancy.

2. *Analysis.*—a. *Efficacy.*

(1) *Animals.* The data available are limited and are of minor relevance in view of data on man.

(2) *Humans.* The general efficacy of live attenuated measles vacines has been well established. With specific reference at Attenuvax, three studies are cited in which 96 to 100 percent of susceptibles serocoverted (N=approximately 180) as measured by the hemagglutination-Inhibition test. In addition, Attenuvax was one of the vaccines represented in studies of outbreaks in 1969–1971 in which vaccination was shown to be 90 to 95 percent protective.

b. *Safety.* Routine tests have been done in animals as required by Federal regulations. No evidence is given that problems have been encountered. The major (neurologic) risks appears to be 2

per million or less and in no instance has the association of neurologic complications with vaccination been more than circumstantial. (See also the generic statement for measles vaccine.)

c. *Benefit/risk.* See generic review.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

References

(1) Landrigan, P. J. and J. J. Witte, "Neurologic Disorders Following Live Measles-Virus Vaccination," *Journal of the American Medical Association,* 223:1459–1462, 1973.

(2) Modlin, J. F., J. T. Jabbour, J. J. Witte, and N. A. Halsey, "Epidemologic Studies of Measles, Measles Vaccine, and Subacute Sclerosing Panencephalitis," *Pediatrics,* 59:505–512, 1977.

(3) McDonald, R., "SSPE (Subacute Sclerosing Panencephalitis). Is Measles Vaccination Promotive or Preventive?", *Clinical Pediatrics,* 16:124–127, 1977.

(4) Krugman, S., "Measles Immunization: New Recommendations," *Journal of the American Medical Association,* 237:366, 1977.

(5) Yeager, A. S., J. H. Davis, L. A. Ross, and B. Harvey, "Measles Immunization. Successes and Failures," *Journal of the American Medical Association,* 237:347–351, 1977.

Generic Review of Mumps Virus Vaccines

Background

Mumps is a relatively benign disease of childhood with a low case fatality rate and usually only a moderate morbidity. Many patients do not manifest parotitis and there is a substantial incidence of asymptomatic infection. The meningoencephalitis occasionally associated with mumps is usually uncomplicated and self-limited. The greatest stimulus for prevention of mumps by vaccine comes from the feared occurrence of orchitis in postpubertal males. While this is documented to occur with a frequency as great as 20 percent (in epidemic situations as occur in the military), the incidence of subsequent sterility is very low.

While live, attenuated vaccines for mumps had been developed in other countries earlier, the only vaccine available in the United States until 1967 was a killed virus preparation, inactivated with formaldehyde and evaluated for potency by its ability to evoke an antibody response in guinea pigs. The efficacy of this preparation is very much in question (see below).

In 1967, a live, attenuated mumps virus vaccine (virus grown in chick embryo cell cultures) was introduced, and since then it has been used widely with clearly demonstrated safety and efficacy.

The Public Health Service Advisory Committee on Immunization Practices emphasizes its recommendation that mumps immunization programs should not be allowed to take priority over more essential ongoing community health activities. However, whatever resources are sufficient, incorporating live mumps vaccine into routine childhood immunization programs is desirable. The combination live virus vaccines which include mumps antigen can be particularly efficient for this purpose. Keeping this in mind, the Panel recommends that it be given at any age over 1 year, especially to children approaching puberty, to adolescents, and to adults, especially males, who have not had mumps or who have no serologic evidence of mumps immunity. Under those circumstances, a single dose subcutaneously is given, with no booster required. It is cautioned that the vaccine does not offer postexposure protection, but in the case of ineffectual exposure it will then offer immunity and will do no harm.

Precautions include severe febrile illnesses, hypersensitivity to vaccine components (egg proteins), leukemia, lymphoma and other generalized malignancies, therapeutic immunosuppression, and pregnancy. No contradictions are specifically listed.

The FDA regulations governing manufacture of live, attenuated mumps virus vaccine include a seed lot system; propagation in chick embryo cell cultures from eggs of flocks free of Rous and avian leukosis viruses as well as fowl pathogens; neurovirulence safety testing in monkeys of seed lots, and safety testing in adult and suckling mice, monkey and human cell cultures, and embryonated chicken eggs, as well as the usual bacteriologic screening; and a minimum potency of 5,000 $TCID_{50}$ per dose. The labeling should include warnings concerning photochemical deterioration as well as dose designation.

Regulations governing manufacture of formaldehyde-inactivated mumps virus vaccines date back to September 4, 1952 and will not be reviewed in detail herein. The most pertinent feature is the potency of the vaccine. As measured by a complement fixation test, at least a 1:16 dilution of test vaccine should yield 4+ fixation against 4 units of mumps immune serum.

Analysis

1. *Efficacy.*—a. *Live attenuated mumps virus vaccine.* There is wide experience with attenuated mumps virus vaccine and excellent documentation of its efficacy. An example is shown in Table 12, taken from Hilleman et al. (Ref. 1).

Table 12.—*Evaluation of Protective Efficacy of Mumps Virus Vaccine Among Initially Susceptible Children—Comparison of Attack Rates for Laboratory-Proved Cases of Natural Mumps Among Vaccinated and Controls*

Time period after vaccination to challenge	Group	Vaccinated cases/risk	Percentage	Unvaccinated cases/risk	Percentage	Efficacy percentage
0 to 10 months	Family	2/29	6.9	50/58	84.7	91.7
	Classroom	2/114	1.8	49/113	43.4	95.9
11 to 20 months	Family	1/14	7.1	22/24	91.7	92.3
	Classroom	1/28	3.6	24/40	60.0	94.1
Total	All	5/174	2.9	133/224	59.4	95.1

Neutralizing antibody was shown to persist for at least 8 years after vacinnation, and protective immunity was retained through the 8 observation years (the attack rates of children exposed to mumps were 0/18 in vaccinies and 27/35 in the unvaccinated).

B. *Mumps vaccine, killed.* Essentially no data are available to document the efficacy of this preparation in the prevention of mumps. A study by Habel in 1951 (Ref. 2), which suggested protection by a killed mumps virus vaccine, used a different preparation, one in which the vaccine was mixed with a peanut oil-beeswax adjuvant. A study by Meyer et al. in 1966 (Ref. 3) used the presently available type of preparation in parents, who were seen when their children had mumps and who themselves had not had the clinical disease. In their group of 176 vaccinees,

there were 14 clinical cases of mumps (8 percent) in comparison to six cases of the clinical disease among 153 controls (3.9 percent).

Thus, no efficacy was demonstrated by this study using two sub-cutaneous injections of 1.0 ml each approximately 1 week apart.

Sood used a current preparation (2 doses of 1 ml each at an interval of 2 weeks) in Gorkha recruits (Ref. 4). There were 51 cases of mumps among 1,000 vaccinees, and 94 among 1,040 controls, giving a coefficient of vaccine effectiveness of 1.4.

Disregarding those cases which occurred within the first 3 weeks, there was a reduction in incidence of mumps in the vaccinated group as compared to the control group (31.0 per 1,00 v. 70.1 per 1,000, or a coefficient of effectiveness of 2.2).

A study to test rapid immunization potential by Friedman et al. (Ref. 5) showed that even a large dose (10 ml) given as a single injection to children resulted in only 17 percent (4/23) seroconversion within 1 week.

2. *Safety.*—a. *Live, attenuated mumps virus vaccine.* Few, if any significant adverse reactions or complications have been associated with delivery of many millions of doses. The Center for Disease Control cites only one serious illness associated with mumps antibody rise within 2 months of immunization. The manufacturer cites, of many millions of doses, the following temporally related incidents: nine cases of encephalitis (0.7 per million), two febrile convulsions, one case each of deafness and visual disturbance.

b. *Mumps vaccine, killed.* Data are sparse. Field trials report a small percentage of febrile reactions. The producers report only one complaint, an undescribed neurological disorder, during the period 1969 through June 1973.

3. *Benefit/risk.*—a. *Live, attunuated mumps virus vaccine.* The benefit/risk ratio is favorable in that there is excellent protection against the disease with virtually no reported short-term complications of vacinnation. While the disease is usually nonfatal it may occasionally be associated with considerable morbidity and occasionally with serious complications. (see Fig. 4)

b. *Mumps vaccine, killed.* While there is apparently very little risk from vaccination with currently available inactivated mumps vaccine products, there is also no demonstrable benefit, resulting in a ratio approaching zero.

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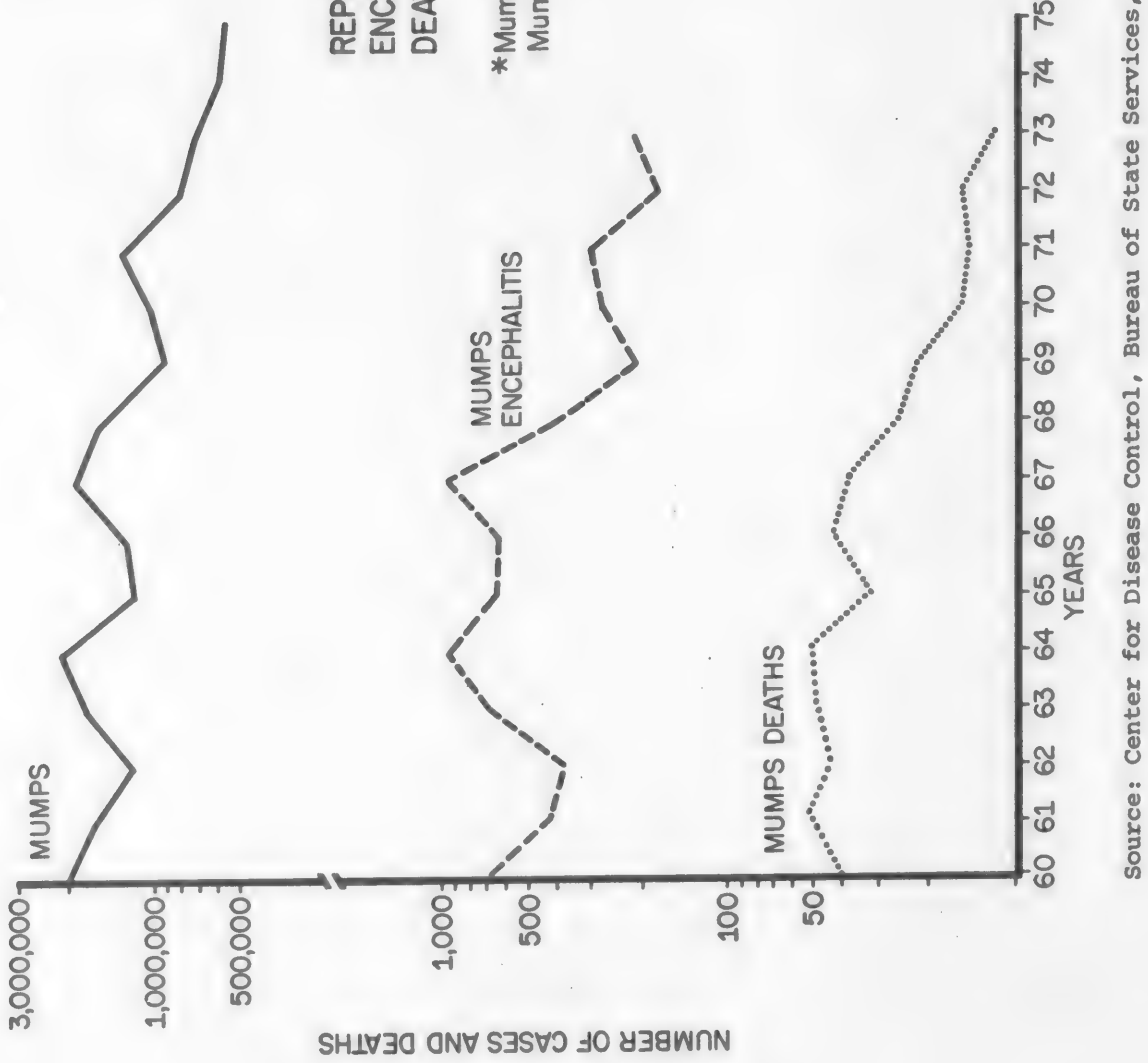
Figure 4

REPORTED CASES OF MUMPS, MUMPS ENCEPHALITIS, AND MUMPS-ASSOCIATED DEATHS, UNITED STATES, 1960-1975*

*Mumps Encephalitis data through 1973
Mumps Deaths data through 1973



Source: Center for Disease Control, Bureau of State Services, Immunization Division.

BILLING CODE 4110-03-C

4. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

Recommendations

1. *Live, attenuated mumps virus vaccine.* This is an excellent biological product and the license should be continued.

2. *Mumps vaccine, killed.* It is recommended that licensure for manfacture of this product be withdrawn in that there is no demonstrable efficacy of the currently available inactivated mumps vaccine and no justification for its continued production.

Review of Individual Mumps Virus Vaccine Products

Mumps Virus Vaccine, Live (Mumpsvax) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* Live mumps virus, Jeryl-Lynn strain, attentuated (B level) by passage in embryonated hens' eggs and in chick embryo cell culture, with the vaccine being prepared from virus grown in the latter medium. Each does of vaccine contains not less than 5,000 $TCID_{50}$ of mumps virus, as stated on the label and in the package insert, and also contains 25 mcg of neomycin per dose.

a. *Recommended use.* The vaccine is indicated for immunization against mumps in children over 1 year of age and adults.

b. *Contraindications.* (1) Pregnancy; (2) Sensitivity to eggs, chicken, chicken feathers, or neomycin; (3) Blood dyscrasias, leukemia, lymphoma, etc; (4) Therapy with ACTH, corticosteroids, irradiation, or other immunosuppressants; (5) Gamma globulin deficiency; (6) Any active infection.

2. *Analysis.*—a. *Efficacy.* (1) *Animals.* See section on human efficacy.

(2) *Humans.* Efficacy is clearly established both in terms of serologic response and in terms of protection (see Table 12). Neutralizing antibody has been shown to persist for at least 8 years after vaccination and protective immunity through at least 6 years (Ref. 6).

b. *Safety.* (1) *Animals.* Routine tests are done as required by Federal Regulations.

(2) *Humans.* There have been few, if any, significant adverse reactions or complications following the administration of the many million doses given thus far. The rate of temporally associated neurologic disease occurring within 30 days after vaccination is less than 1 per million, which is similar to or less than the expected rate in unimmunized children of a similar age.

c. *Benefit/risk.* See generic review.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions.*—a. *Critique.* This is a safe and effective product in children. There are inadequate data regarding protective effectiveness in susceptible adults (e.g., military recruits) but safety and antigenicity have been established in adults.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Mumps Virus Vaccine (Inactivated) Manufactured by Eli Lilly & Co.

1. *Description.* This preparation is a suspension of killed mumps virus derived from the extra-embryonic fluids of virus infected chick embryos. The virus is concentrated and purified by differential centrifugation inactivated with formaldehyde solution, 1:2,000, and suspended in isotonic saline containing 0.05 molar glycine. Thimerosal solution, 1:10,000, is used as the preservative.

a. *Recommended use.* The vaccine is intended for active immunization against mumps. The primary immunization consists of two injections given 1 to 4 weeks apart, and a booster injection is given 6 months to 1 year later. Emphasis is on prevention of mumps in young adults, particularly those in segregated populations (e.g., military recruits, medical students, and nurses). Routine administration of vaccine to all susceptible individuals is recommended, with susceptibility being determined by use of skin test antigen. Its use is also recommended to abort epidemics. Use of the vaccine for routine immunization before adolescence is not recommended.

b. *Contraindications.* (1) A history of egg sensitivity;

(2) Immune individuals;

(3) Therapy with ACTH, corticosteroids or other immunosuppressants.

2. *Analysis.*—a. *Efficacy.* (1) *Animal.* The minimum acceptable antigen concentration is that which will give complete (4+) fixation of complement at a 1:16 dilution against 4 units of a FDA reference antiserum. One batch in this submission is shown to have a titer of 1:64. The submission also includes data on a recent (1973) lot tested in guinea pigs (1 ml given intraperitoneally); pooled sera from 10 such guinea pigs had a CF titer of 1:32 against the 4 units of antigen required.

(2) *Human.* The manufacturer submitted no data concerning the effectiveness of his current product; the literature cited as pertaining to effectiveness dealt with a different product, incorporated into a peanut oil-beeswax adjuvant.

b. *Safety.* (1) *Animal.* The submission states that the product passes all safety tests.

(2) *Human.* The product is safe with less than 1 complaint per 100,000 doses of vaccine distributed.

c. *Benefit/risk ratio.* While there is no evidence of direct, substantial risk, there is also no evidence that the vaccine is of benefit, since it is poorly antigenic and offers no sustained protection.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP. The labeling in the submission to the Panel is considered inappropriate because one must read the fine print to discover that this is inactivated mumps vaccine, whereas the label should clearly indicate inactivation.

3. *Conclusions.*—a. *Critique.* Use of this vaccine requires prior determination of susceptibility in the recipient, but with the currently available antigens, the present skin test is not a reliable indicator of immunity as reported in the **Federal Register** of September 30, 1977 (42 FR 52674).

It seems highly unlikely that use of serological tests to determine susceptibility in exposed adults would be appropriate or timely, and the expense, even if such tests are available, would not be justified to attain the minimal protection that might be offered by inactivated vaccine.

The Panel concludes that the indications, as given, are inappropriate. Inactivated mumps virus vaccine is only marginally effective, and is of very limited usefulness.

b. *Recommendation.* Given the availability of live mumps virus vaccine, there seems to be no good justification for the continued production of inactivated mumps vaccine. Consequently, the Panel recommends that this product be placed in Category II and that appropriate license(s) be revoked because there are compelling reasons to assume a lack of

effectiveness and an unsatisfactory benefit-risk ratio for this product.

The Panel is aware that inactivated mumps virus vaccine is used to hyperimmunize donors as a source of immune plasma for the production of mumps immune globulin (human). This vaccine usage is discussed in the section dealing with mumps immune globulin.

Mumps Vaccine (Killed) Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* The vaccine is prepared from the allantoic fluid of embryonated hens' eggs infected with mumps virus. The virus is concentrated, inactivated with formaldehyde and ethylene oxide, and suspended in a 0.1 M sodium phosphate buffered solution with 1:10,000 thimerosal added as a perservative. The actual viral content is not stated.

a. *Recommended use.* To protect susceptible individuals who have been exposed to infection, the vaccine should be given 2 to 3 days after such exposure.

The recommended immunizing dose for children and adults is two injections of 1.0 ml each, administered either subcutaneously or intramuscularly. The interval for optimal immunizations is not known, but 1 to 4 weeks between injections is suggested.

b. *Contraindications.* (1) Presence of tuberculosis, debilitating disease, latent or active infections;

(2) Sensitivity to eggs, chicken, or chicken feathers.

2. *Analysis.*—a. *Efficacy.* (1) *Animals.* Potency is measured by a compliment fixation test. At least a 1:16 dilution of the test vaccine should give complete (4+) fixation of complement against four units of a FDA Reference Antiserum Seven guinea pigs were each given 1 ml of vaccine intraperitoneally, bled 3 weeks later and the sera tested for antibody by complement fixation; a serum CF titer of 1:32 against 4 units of antigen (equal to minimum requirements) was shown in protocols provided for a recent batch.

(2) *Humans.* The submission incorporates references pertinent to the efficacy of killed mumps vaccine. These are discussed with pertinent data, under the generic review. The Panel knows of no evidence that effective protection can be induced within 2 to 3 days after exposure as is implied by the recommended use of the product within this interval. Sood's data (Ref. 4) suggest that a 3 to 6 week interval is necessary and show that absolutely no protection is afforded within 3 weeks postvaccination, evidently even after the second dose.

No procedure for determining susceptibility is given. It does not seem justified to recommend general vaccination of children except where special conditions exist (e.g., large groups housed in institutions, summer camps, orphanages, etc.) and vaccination is repeated at annual intervals to keep the antibody titer at an adequate level.

b. *Safety.* (1) *Animals.* The tests reported in the submission were satisfactory.

(2) *Humans.* Field trials report the occurence of a small percentage of febrile reactions; the producer reports only one complaint, an undescribed neurological disorder during the period 1969 thru June 1973.

c. *Benefit/risk.* While there is no evidence of a substantial direct risk, there is also no evidence of benefit, since the vaccine is poorly antigenic and offers no sustained protection.

d. *Labeling.* The labeling is inappropriate because it is not immediately obvious that the product is an inactivated mumps virus vaccine. The Panel also considers the indications to be inappropriate (see Recommendation). Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and the updated recommendations of ACIP.

3. *Conclusions.* a. *Critique.* This product is not recommended by ACIP. As detailed above, there is no evidence that this product is efficacious. In view of the availability of an effective attentuated mumps virus vaccine, there seems little or no need for this product.

b. *Recommendation.* There is no good justification for the continued production of inactivated mumps virus vaccine, and the Panel recommends that this product be placed in Category II and that appropriate license(s) be revoked because there are compelling reasons to assume lack of effectiveness and an unsatisfactory benefit-risk ratio for this product. The Panel is aware that inactivated mumps virus vaccine is used to hyperimmunize donors as a source of plasma for the production of mumps immune globulin (human). This vaccine usage is discussed in the section dealing with mumps immune globulin.

References

(1) Hilleman, M. R., E. B. Buynak, R. E. Weibel, and J. Stokes, Jr., "Live, Attenuated Mumps-Virus Vaccine," *The New England Journal of Medicine,* 278:227–232, 1968.

(2) Habel, K., "Vaccination of Human Beings Against Mumps: Vaccine Administered at the Start of an Epidemic. I. Incidence and Severity of Mumps in Vaccinated and Control Groups," *American Journal of Hygiene,* 54:295–311, 1951.

(3) Meyer, M. B. et al., "Evaluation of Mumps Vaccine Given After Exposure to Mumps, With Special Reference to the Exposed Adult," *Pediatrics,* 37:304–315, 1966.

(4) Sood, Y. P., "A Study of a Field Trial of Formalin Inactivated Mumps Vaccine in the Control of Mumps in Gorkha Recruits," *Indian Journal of Medical Research,* 56(2):234–242, 1968.

(5) Friedman, R. M., A. I. Holtz, S. Baron, S. Silbergeld, and C. E. Buckler, "Studies on Rapid Immunization with Mumps Vaccine," *American Journal of Hygiene,* 78:269–274, 1963.

(6) Weibel, R. E., E. B. Buynak, A. A. McLean, and M. R. Hilleman, "Long-Term Follow-up for Immunity After Monovalent or Combined Live Measles, Mumps, and Rubella Virus Vaccines," *Pediatrics,* 56:380–387, 1975.

Generic Review of Rubella Virus Vaccine

Background

Infection with rubella virus is generally a benign self-limiting illness of childhood. However, infection of a susceptible woman during the first trimester of pregnancy may give rise to transplacental infection of fetal tissues and result in serious congenital abnormalities. The recognition of this association between rubella infection and congenital disease was first made in Australia by Gregg in 1941. (See Ref. 1 for one discussion of this association.) Since then, his observations have been confirmed during the course of several rubella epidemics, including the United States epidemic of 1964 which resulted in a large number of infants with congential rubella syndrome. The prevention of rubella epidemics and their sequelae became possible with the development of attenuated live rubella virus vaccine. The vaccine was licensed in June 1969 and more than 70 million doses have been administered. The data in Table 13 indicate that as many as 80 percent of children 5 to 9 years old have natural or vaccine-acquired immunity.

Table 13.—*Rubella Immunization Status of Children in Age Groups 1–4 and 5–9; United States 1965–72*

[Population in thousands]

Year	Net dosage of vaccine[1] distributed	1–4 year age group percent with			5–9 year age group percent with		
		Population	Vaccine	Infection	Vaccine/infected	Population	Vaccine	Infection	Vaccine/infected
1965		16,502		26.5		20,361		56.0	
1966		16,091		25.1		20,436		51.8	
1967		15,552		20.2		20,862		46.8	
1968		14,994		18.5		20,856		44.2	

Table 13.—*Rubella Immunization Status of Children in Age Groups 1–4 and 5–9; United States 1965–72*—Continued

[Population in thousands]

Year	[illegible] dosage of vaccine[1] distributed	1–4 year age group percent with				5–9 year age group percent with			
		Population	Vaccine	Infection	Vaccine/ infected	Population	Vaccine	Infection	Vaccine/ infected
1969		14,393		16.7		20,773		40.4	
1970	[illegible][2]	14,123	37.2	14.4	47.3	20,421	46.5	31.8	[illegible]
1971	[illegible]	14,112	51.2	13.9	59.4	19,799	63.2	28.0	77.8
1972	7.0	13,905	[illegible]	12.3	63.3	18,552	[illegible]	25.7	79.5

[1] Biologics Surveillance (million).
[2] Total doses (not) distributed from June 1969 through December 1970.
Source: CDC, Bureau of Epidemiology.

The purpose of rubella vaccination is primarily to prevent rubella embryopathy. The direct approach to this goal would be to immunize all women before they become pregnant. The impossibility of insuring that any given women was not pregnant and an increased rate of side effects (joint symptons) in women rendered this direct approach impractical on a public health level. Because children, on the basis of serologic and epidemiologic studies, were an important primary source of virus excretion to infect pregnant women, rubella vaccine policy was initially to immunize children of all ages. Women of child-bearing age, if not pregnant, are of equal importance and all others are of significantly lower priority to receive vaccine.

The Public Health Service Advisory Committee on Immunization Practices for rubella vaccine recommends live rubella virus vaccine for all children between the age of 1 year and puberty. It should not be administered to infants less than 1 year of age because of their possible failure to respond to vaccination.

Priority for immunization should be given to children in kindergarten and elementary school because they are a major source of virus dissemination in the community. For optimum program effectiveness, it is essential that immunization activities be developed to ensure ongoing, routine immunization of preschool children as well. A history of rubella is not reliable; therefore, all children should receive vaccine.

It is desirable for rubella vaccination programs to include adolescent girls and adult women. Because of the precautions which must apply, potential vaccinees in these groups should be considered individually. They should receive vaccine only if they are shown to be susceptible by serologic testing and if they agree to prevent pregnancy for 2 months after immunization.

To accomplish such extended use of rubella vaccine, accurate serologic testing capabilities should be improved. With sufficient laboratory services available, there is merit in undertaking prenatal or antepartum screening for rubella susceptibility and, if appropriate, immunization in the immediate postpartum period. *Pregnant women should not under any circumstances be given vaccine.*

Immunization of adolescent or adult males is of lower priority; however, it may be a useful practice in the prevention or control of outbreaks of rubella in circumscribed population groups.

There is no evidence that live rubella virus vaccine given after exposure will prevent illness. There is, however, no contraindication to immunizing children already exposed to natural rubella. Similarly, there is no harm in vaccinating persons who have had rubella.

The contraindications are as follows:

1. *Pregnancy.* Live rubella virus vaccine is contraindicated.

2. *Altered immune states.* Attenuated rubella virus infection might be potentiated by severe underlying disease such as leukemia, lymphoma, or generalized malignancy, and when the immunologic response has been suppressed with steriods, alkylating drugs, antimetabolities, or radiation. Such patients should not be given live rubella virus vaccine.

3. *Febrile illness.* Immunization should be postponed until the patient has recovered.

4. *Hypersensitivity to vaccine components.* Theoretically, rubella vaccine should not be given to children clearly hypersensitive to the animals from which cells are derived for use in vaccine production or to other components of the vaccine. To date, there have been no documented reports of serious reactions to rubella vaccine clearly attributable to hypersensitivity.

Now that the vaccine is in general use, accurate diagnosis and reporting of congenital rubella syndrome and vaccine complications have become more important than ever. All cases of birth defects suspected of being related to rubella should be thoroughly investigated and reported. There should also be continuing followup of women inadvertently vaccinated during pregnancy.

A number of aspects of FDA regulations for manufacture of Rubella Virus Vaccine, Live, warrant emphasis or comment. (See 21 CFR 630.60).

1. *Strains.* Vaccine strains must be identified by historical records and antigenic specificity. Field studies must document that the strain is safe, potent, and noncommunicable to susceptible, unvaccinated persons.

2. *Cell substrate.* There are some aspects of testing cell substrates for extraneous agents or indigenous viruses, especially in the duck embryo system, which should be updated.

3. *Potency.* Potency requirements are regularly met by the manufacturer. Photoinactivation is applicable to this vaccine as well as to other viral vaccines and is a factor in storage of the products.

4. *Production procedures.* A defined seed-lot system is in effect; five passages from the master seed are permitted.

5. *Safety tests.* Tests in monkey kidney cell cultures for cytopathic viruses are probably not as important as tests employing human cells. The inoculation of embryonated eggs should specify incubation period and subpassage requirement of tests to be employed.

Analysis

1. *Efficacy.*—a. *Animals.* Not applicable.

b. *Humans.* Immunization against rubella is directed toward prevention of infection in the pregnant woman since, during the early months of pregnancy, the virus may cross the transplacental barrier to infect the fetus, with the risk of embryopathy. The effectiveness of the vaccine has been evaluated in a number of ways. First, in early experimental studies high passage level virus was shown to produce a modified infection and to be immunogenic in the rhesus monkey. The antibody response produced by such an infection protected animals against subsequent challenge with the natural virus. Second, the vaccine has been shown to protect vaccinees exposed to wild virus under natural conditions; i.e., in rubella epidemics, vaccinees did not develop clinical disease whereas cases of rubella were observed in seronegative, previously unvaccinated persons.

The most direct evidence of effectiveness would be through epidemiologic analysis of the incidence of the disease and on the ability of the vaccine to reduce the incidence of congenital defects associated with the rubella syndrome. The following is

based on data extracted from CDC reports (Ref. 1) and a review of the current literature on rubella. This epidemiological approach to an evaluation of the effectiveness of rubella vaccine in the United States is complicated by several variables: (1) surveillance is inadequate for both the clinical disease and the congenital rubella syndrome; (2) spread of the virus and the development of epidemics are somewhat unpredictable; and (3) the increasing use of serological screening, followed by abortion for proven rubella infection in the first trimester of pregnancy, could be responsible for the decreased number of infants born with congenital rubella.

Figure 5 shows reported cases of rubella by year from 1966 through 1973 and Figure 6 shows the reported cases by 4-week periods 1969 through 1975.

Although the accuracy and completeness of reporting of rubella vary considerably in different areas of the country, the data available do appear sufficient to permit analysis of disease patterns and trends in the United States. Thus, despite yearly and regional variations, the great preponderance of States reported (see Fig. 5) a decline in rubella from 1971 to 1972, with the total number of cases showing a decline of 43 percent (from 45,086 to 25,507) over this 1 year and a decline of 50 percent from the average number of cases reported in each of the years 1967 to 1971. From 1969, when rubella vaccine was first licensed (see Fig. 6A), the incidence of rubella has decreased steadily through 1975 with only slight upward fluctuations in 1973 and 1975.

The appearance of epidemic rubella every 6 to 9 years had led to predictions that another significant epidemic would occur in the early 1970's. No such epidemic occurred, and the incidence of rubella over the last 46 years (shown in Fig. 7) suggests that use of the vaccine since 1969 has affected the 7- to 9-year cycling of rubella epidemics in this country.

Data on the age incidence of rubella collected from four areas, viz., Illinois (exclusive of Chicago), Chicago, Massachusetts, and New York City for the 4-year interval 1969 to 1972 have been compared with similar data from the same areas for the 5-year period 1963 to 1967. The observed decrease in incidence was found to give a generally symmetrical pattern in each age group; also, the accumulated percentages of rubella cases by age for the pre- and postvaccination periods showed no significant difference. While absence of a displacement in the age-specific incidence curve may represent an unusual situation in these four study aeas, a more likely interpretation is that immunization of school-age children has lead to a diminished activity of rubella virus in all age groups.

While the information available on the congenital rubella syndrome is not entirely satisfactory, the data suggest that there has been a decline in this syndrome coincident with widespread immunization and with the concomitant decline in the incidence of reported rubella.

The Center for Disease Control, in 1969, established a National Registry for the Congenital Rubella Syndrome, but the reporting of cases has been less than satisfactory. Of some 284 case reports received by the Registry by July 1974, only 237 represent children born in 1969 or later. Eleven of the 50 States have reported no cases and certain States (California, Colorado, and Louisiana) account for a disproportionately large number of cases in the Registry (Ref. 3). In figure 8 the reported incidence of rubella is given by 4-week periods from 1969 to 1975 in order to provide a background for the lower graph which depicts the cases of congenital rubella syndrome (CRS) reported to the Registry by date of birth since 1969.

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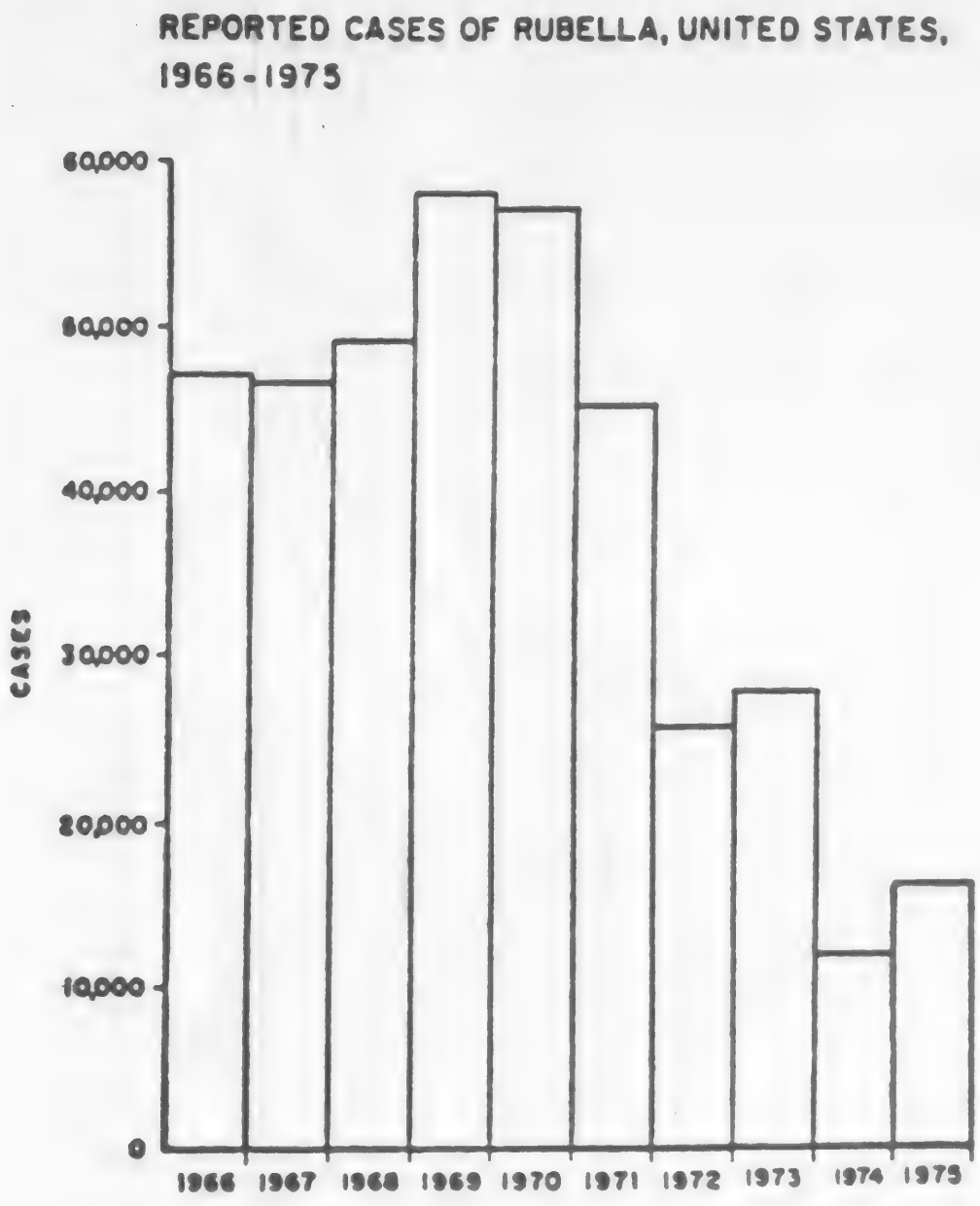
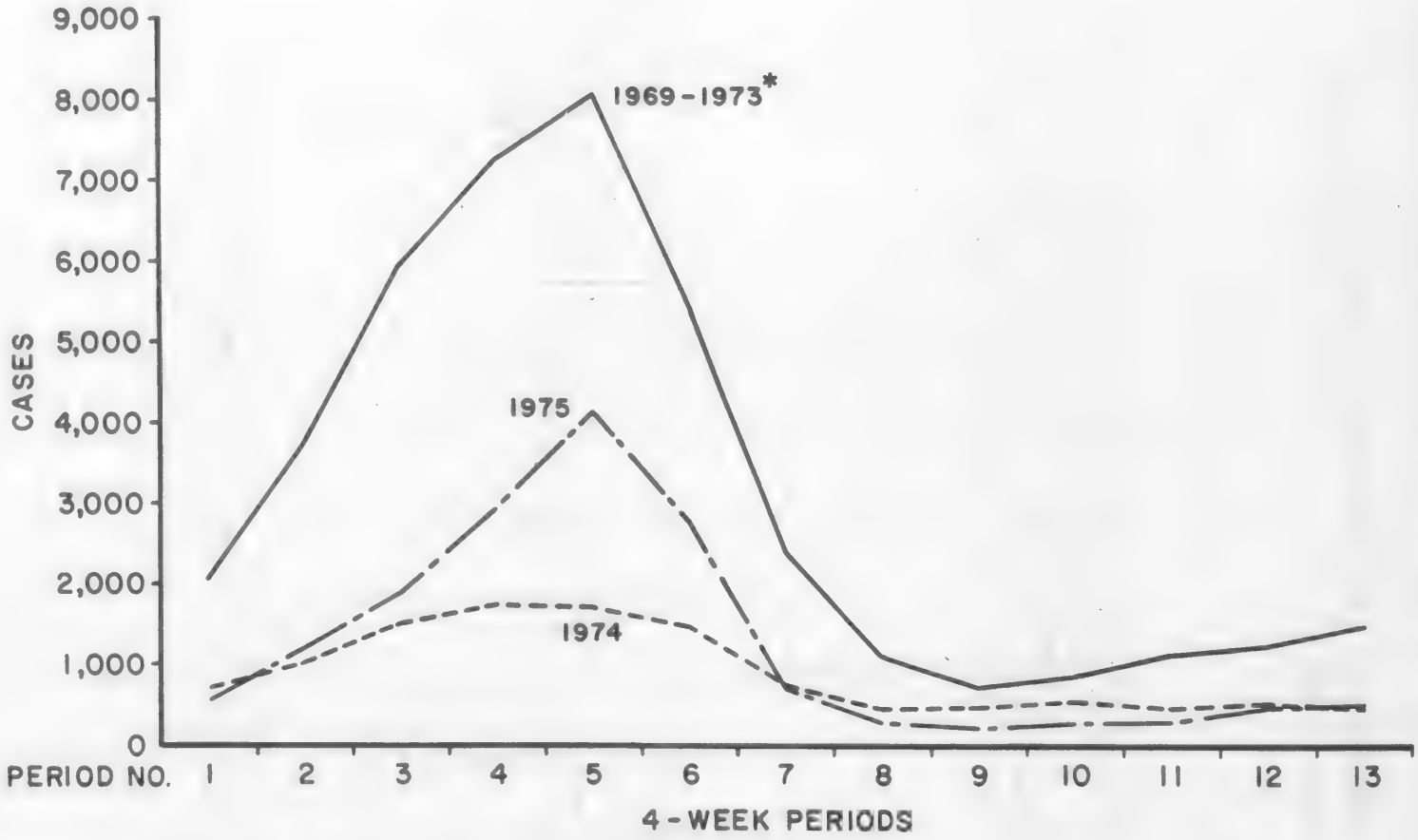
Figure 5



Source: From Rubella Surveillance Report, CDC, August 1976

Figure 6

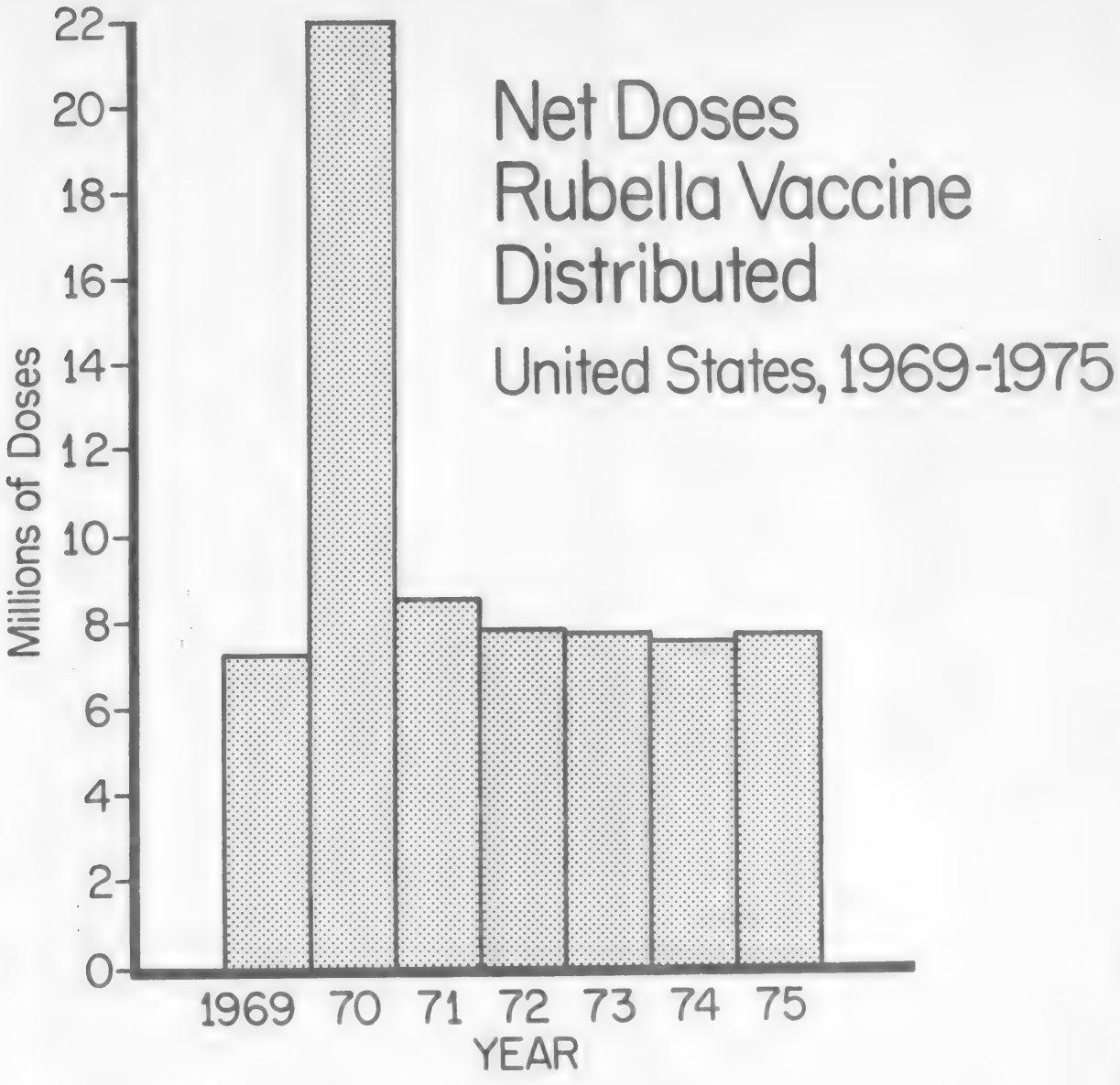
REPORTED CASES OF RUBELLA, BY 4-WEEK PERIODS, UNITED STATES, 1969*-1975



*5-YEAR AVERAGE USED FOR 1969-1973

Source: Center for Disease Control, Bureau of Epidemiology.

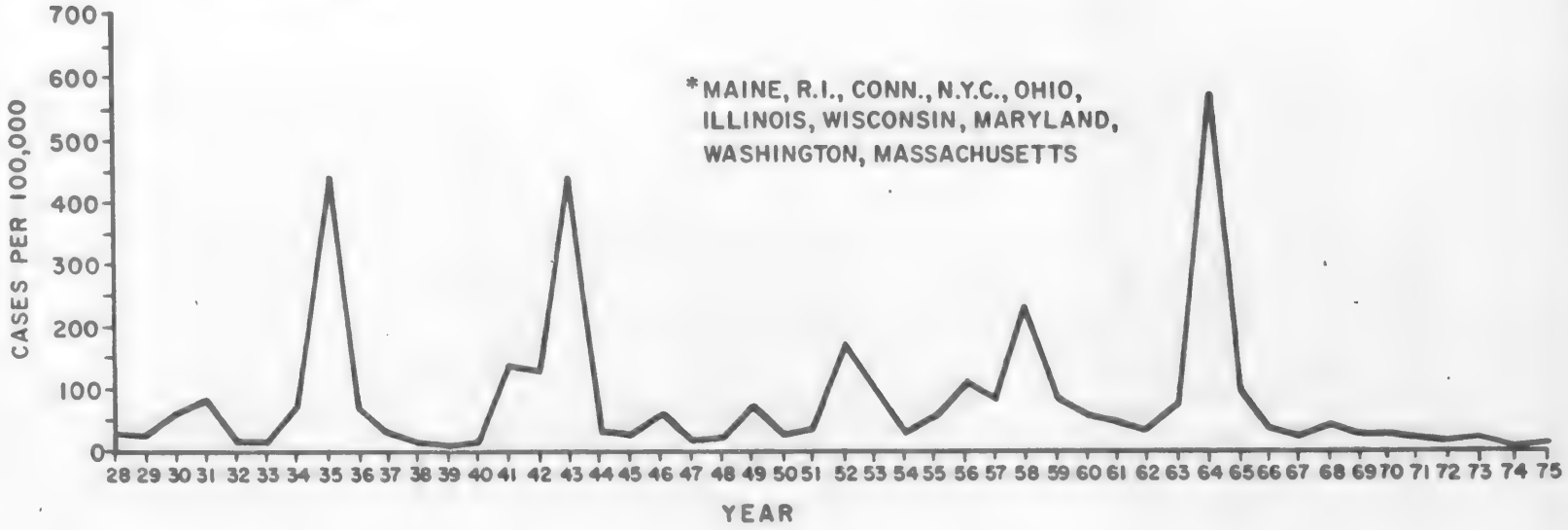
Figure 6A



Source: Center for Disease Control

Figure 7

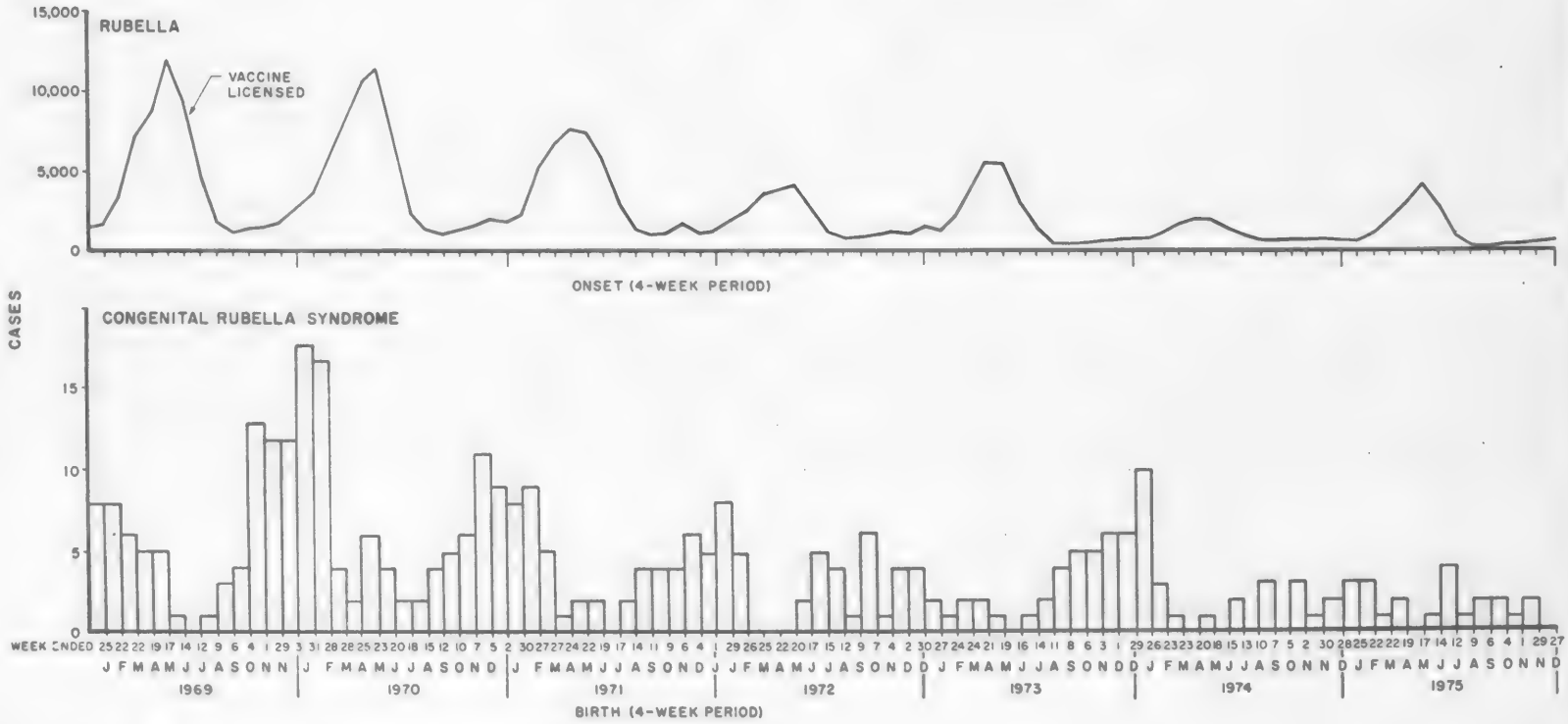
RUBELLA INCIDENCE, TEN SELECTED AREAS*, UNITED STATES, 1928–1975



Source: Center for Disease Control, Bureau of Epidemiology.

Figure 8

CASES OF RUBELLA*, BY PERIOD OF ONSET, AND OF CONGENITAL RUBELLA SYNDROME, BY PERIOD OF BIRTH,** USA, 1969-1975



* OFFICIAL TELEGRAPHIC REPORTS FROM STATES AND AREAS

** FROM CRS REGISTRY

Source: Center for Disease Control, Bureau of Epidemiology.

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Peaks in the number of births with CRS are evident at 7 to 9 months after the peaks in rubella virus activity and the number of CRS cases appears to have declined since 1969. It is obvious that reporting of the congenital rubella syndrome must be improved, but despite this, Figure 8 suggests that there has been a decline in the number of cases of congenital rubella syndrome.

The overall evidence presented by all of the studies published thus far on the persistence of antibodies indicates that rubella HAI antibody titers are stable for at least the first 2 to 4 years after vaccination, and that the pattern of antibody decline is the same as that observed after the natural disease.

Subclinical reinfection following exposure to wild-type rubella virus has been reported to occur both after natural immunity and after vaccine-induced immunity. Studies in small groups of institutionalized children or young adults (military recruits) have shown the occurrence of a rise in antibody titer in 2.5 to 10 percent of children with natural immunity, compared with antibody increases in 3.5 to 80 percent of children and young adults exposed to wild-type rubella virus at varying intervals after vaccination. Thus far, the only study concerned with an urban community which experienced a rubella outbreak 9 months after a vaccination campaign reported rises in antibody titer in 12.7 percent of the population vaccinated with HPV–77 DE–5, and in 11.6 percent of susceptibles over the same time period, thus showing that rubella virus had circulated through this community.

The major concern regarding reinfection is related to its significance during pregnancy. Would the fetus of a reinfected women be at risk of infection by the natural virus? The evidence thus far does not support the probability of such an occurrence. Thus, in one study (Ref. 4) it was found that vaccinated children exposed in an epidemic did not become viremic, and the titer of virus in the pharynx and the duration of shedding were both markedly less than that seen in susceptible children studied under the same conditions. Hence, it seem unlikely that in a comparable situation in a reinfected pregnant woman, virus would reach the fetus. To date, there are no published data concerning reinfection of pregnant women vaccinated earlier. Reinfection of women with naturally acquired immunity has been reported, but the number of cases involved is small and the diagnosis has been subject to debate. On balance, it seems that protection of the fetus will be assured if circulating antibodies are present. Definitive resolution of this question obviously must await further study.

Occasional instances of clinical reinfection in individuals either with a natural immunity or a vaccine-induced immunity have been reported but these seem to be of little public health impact.

In rubella, as in measles and poliomyelitis, periodic reinfection may be a mechanism for the maintenance of high titers of antibody. It is well documented that the vaccine has been effective for the prevention of clinical disease in persons who have been adequately immunized, and it is assumed that the same factors which prevent clinical disease following reinfection will also prevent or greatly reduce fetal infection.

Appropriate use of the vaccine is essential to achieve the purpose for which it was developed, viz., to prevent congenital rubella.

2. *Safety.* The concerns for safety are related to toxic, infectious, allergic, or oncogenic factors. The experience with the vaccine thus far attests to its safety over the short term. Field test criteria include prospective enlistment of 5,000 vaccine recipients (with appropriate controls) for long-term followup to detect rare events associated with vaccine administration and/or to detect vaccine-associated events with long latent periods.

a. *Animals.* Tests in animals exclude adventitious viruses. See the preceding section refering to FDA regulations, and also specific product reports. Tests for oncogenicity in animals are negative.

b. *Humans.*

(1) *Adverse reactions.* The primary concern is with joint reactions. A compilation of long persisting joint reactions suggests they can occur but are not common and, in the great majority of cases, symptoms eventually disappear.

The capacity to produce transient arthralgia and arthritis is a property of the virus strain and varies with the age and sex of the recipient. In studies involving children the rates were as follows: the canine kidney vaccine, which is no longer licensed, produced reaction rates between 8.1 percent and 20.7 percent in five clinical studies; the Cendehill vaccine, prepared in primary rabbit kidney cells, produced rates of 5.1 percent and 8.9 percent in two studies; with the HPV–77 vaccine prepared in duck embryo cell cultures, the reaction rates ranged between 1.8 percent and 7.6 percent (six studies). Thus, there is probably no significant difference between the Cendehill and HPV–77 strains in this regard.

These symptoms occur more frequently in adults and more in women than in men, thereby further complicating patient acceptance of these products. No other reactions, including allergic, occur with enough frequency to permit a meaningful evaluation.

(2) *Vaccination of women shortly before or after conception.* One of the hazards of administering rubella vaccine to women of child-bearing age is the potential infection of the fetus by the vaccine virus.

In a report of rubella surveillance the CDC tabulated observations on 343 women who were vaccinated shortly before or after conception (Ref. 4). The pertinent data are given in Table 13a, and show that of the 172 live infants born to this group of mothers (of whom 38 were known to be susceptible to rubella), none showed evidence of rubella embryopathy. However, this same study at CDC clearly demonstrated (as have others) that the vaccine strains can infect fetal tissues and induce histologic changes analagous to those observed to follow infection with wild virus; this is illustrated in Table 14.

Table 13a.—*Outcome of Pregnancies in Women Receiving Rubella Vaccine Shortly Before or After Conception*

Prevaccination immunity status	Number of cases	Outcome of pregnancy				
		Abortion		Delivery of live infants	Unborn	Virus isolate
		Therapeutic	Spontaneous			
Susceptible	70	28	3	36	1	6
Immune	14	1	0	13	0	0
Unknown	259	116	13	121	8	3
Total	343	145	16	172	9	9

Source: Modlin, J. F., K. Hermann, et al., *New England Journal of Medicine, 294:972-974, 1976.*

Table 14.—*Characteristics of Patients With Rubella Vaccine-Like Virus Isolated From Therapeutic Abortion Specimens*

Pre-vaccination immunity status	Gestation at abortion (weeks)	Interval between vaccination and abortion (weeks)	Tissues positive for rubella virus
Unknown	14	16	Fetal eye, placenta.
Unknown	13	2	Fetal kidney, placenta.
Susceptible	6	6	Placenta.
Susceptible	8	5	Decidua.
Unknown	10½	9½	Decidua, placenta.
Susceptible	13½	4	Placenta.
Susceptible	13	20	Fetal eye.
Susceptible	18	12	Fetal bone marrow.

Source: Rubella Surveillance Report, CDC, November 1973.

It should be noted that no differences between the licensed strains were detected in these studies. The actual risk of vaccine virus-induced congenital disease is still unknown. While the recovery of virus from the products of conception suggests a pathogenic potential, the absence of such disease in live born infants of vaccinated susceptible mothers suggests that the risk is at least an order or magnitude less than that associated with wild disease. Continued surveillance in this area is needed.

3. *Benefit/risk.* The cost of providing the necessary health care for, and the support of, 4,000 blind/deaf children with rubella syndrome in the New York City area from the 1964 epidemic is estimated to be $30 million per year for at least another 20 years. This is only a partial cost, since, nationwide, as many as 20,000 infants were recorded to have congenital rubella as an aftermath of that epidemic. The absence of a major epidemic since 1964, the decline in the incidence of rubella, and the decrease in reported cases of rubella empryopathy are clear evidence of the benefits; while the exact contribution of the licensed vaccine to this benefit is not quite as clear as one would like, the Panel concludes that the vaccine deserves primary credit for the alterations that have been noted in the epidemiology of rubella.

The risk of rubella vaccine is limited to two areas: (1) transient arthralgia and arthritis, especially in postpubertal recipients, and (2) accidental vaccination of pregnant women. These factors tend to increase the difficulties of administration to adults but are of little practical significance in vacination of children. All other risks are theoretical and there is no means of including them in calculations which are already imprecise. While the benefit-risk ratio of rubella vaccine is probably not as high as that of measles or poliovirus vaccine, it is already great enough to more than justify its continued licensure.

4. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and the updated recommendations of ACIP.

Recommendations

1. The labeling and package inserts of rubella vaccines should be continuously updated to reflect ACIP recommendations.

2. The Panel suggests that the ACIP recommendations for use of the vaccine in women of child-bearing age be phrased positively, and that specific conditions for their immunization be given, as in the following example: "A high priority adult group for immunization are postpartum women shown to be susceptible to rubella by serological testing. Postpartum females who have not been tested can also be immunized; in either case, women should agree to prevent pregnancy for 2 months after immunization. Any nonpregnant woman of child-bearing age who agrees to prevent pregnancy for 2 months also should be given vaccine."

3. Encourage support of continued and more complete rubella surveillance by CDC.

Review of Individual Rubella Virus Vaccine Products

Rubella Virus Vaccine, Live (Meruvax) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* The vaccine is prepared from the duck-cell adapted HPV–77 strain; the virus is grown in duck embryo cell cultures. Each dose (0.5 milliliters) of the reconstituted vaccine contains not less than 1,000 $TCID_{50}$ of rubella virus in terms of FDA reference rubella vaccine, and each also contains 25 mcg of neomycin. The vaccine and the diluent contain no preservative.

a. *Recommended use.* See the generic review.

b. *Contraindications.* See the generic review.

2. *Analysis.* a. *Efficacy.*

(1) *Animals.* No data were submitted by the manufacturer. However, this is of minor relevance in view of the experience in man.

(2) *Humans.* This vaccine was shown to produce seroconversion in approximately 95 percent of vaccinees in clinical trials performend in support of the license application. As concerns the persistence of antibody following inoculation of the vaccine, and specifically with respect to HPV–77 DE–5, i.e., Meruvax vaccine, Weibel et al. (Ref. 5) reported in 1972 on the hemagglutination-inhibiting antibody determinations in a group of 79 children; there was a slight decline in antibody level 2½ years after vaccination and none of the children had become seronegative. Weibel et al. (Ref. 6) reporting on a 5½ year followup the longest to date, found that the titer patterns in children given live attenuated HPV–77 virus were similar to those noted after natural infection, a good indication that the vaccine produces a durable immunity in terms of the humoral antibody response.

b. *Safety.*

(1) *Animals.* The tests employed to ensure the safety of the vaccine for man from the standpoint of adventitious agents, viral or other, are the usual ones demanded by the Bureau of Biologics. However, although precautions are taken to utilize eggs free of avian leukosis virus, the reviewers did not find any mention of the duck infectious anemia virus (DIAV) either as to its recognition that this agent may occur in duck eggs or its possible significance.

(2) *Humans.* From the standpoint of adverse reactions, it is recommended, as mentioned above, that live attenuated rubella virus vaccine not be administered to persons with sensitivities to duck or chicken tissues or feathers, that it not be administered to persons with malignancies or those under treatment with immunosuppressive drugs, nor to individuals with acute febrile illnesses, such as acute respiratory disease. Above all, it should not be administered to pregnant women because of the potential, but as yet unknown, teratogenicity of the attenuated virus.

Although rubella virus has been recovered from the pharynx of institutionalized children who were reinfected, titers of the virus that was shed were very low and a viremia was not demonstrated. The significance of subclinical reinfection in terms of viral transmission, either person-to-person in an epidemic or from the reinfected mother to the unborn child, remains to be determined; however, the low titers of virus involved and the apparent absence of viremia suggest that the hazards of transmission are minimal.

With respect to Meruvax live attenuated rubella virus vaccine, many million doses were distributed over the period June 1969 through December 1972. The most significant of the reported experiences are those involving the nervous system and the most frequently reported reactions were arthralgia and arthritis, as indicated in the following tabulation:

Types of disorder	Number of patients	Reports per million
Polyneuritis	1	0.125
Convulsion	1	<0.1
Febrile convulsion	1	<0.1
Encephalitis	4	0.17
Myelitis	1	0.125
Arthralgia	22	0.9
Arthritis	13	0.54

According to Merck Sharp & Dohme, the above tabulation lists reported reactions which were temporally associated with vaccination, but a relationship between the vaccination and the reaction has not been established. This method of surveillance for adverse reactions, i.e., reports to the manufacturer, obviously grossly underestimates the true incidence of certain adverse reactions, e.g., arthralgia. Occasionally, mild fever may be encountered as may such local reactions as erythema, induration, tenderness, and regional adenopathy.

Transient arthralgia and arthritis, which are common occurrences in natural natural rubella in adult women, have been noted 2 to 4 weeks after vaccination in up to 40 percent of susceptible women. Such reactions are fewer (7 percent) and milder in females between 13 and 21 years of age. Rarely, a more severe arthritis with joint effusion has occurred. Transient arthralgia and arthritis may occur in nonimmune males, but the incidence is lower than in women.

c. *Benefit/risk.* Transient arthralgia and arthritis, both common occurrences in adult women with naturally acquired rubella, have been reported in up to 40 percent of susceptible women who received the vaccine. These are the major reactions encountered; the others, as tabulated earlier in this report are of comparatively infrequent occurrence. The vaccine, although associated with troublesome and painful arthralgias and arthritis, is essentially free of serious complications, such as those of the central nervous system, so that in weighing benefit against risk, the vaccine in the judgment of the Panel is acceptable. More importantly, there is accumulating evidence that the vaccine is reducing the incidence of natural rubella and there is, at the present time, suggestive evidence that the congenital rubella syndrome is also declining.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription durgs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions—recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Rubella Virus Vaccine, Live (Cendehill Strain) (Cendevax) Manufactured by Recherche et Industrie Therapeutiques, S.A.

1. *Description.* According to the package insert:

When reconstituted, 'Cendevax' is a suspension of the 'Cendehill' strain of live, attenuated rubella virus. The vaccine in prepared by propagation in primary cultures of rabbit kidney cells. Each dose (0.5 ml) of 'Cendevax' contains the equivalent of not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of the NIH reference rubella vaccine, and not more than 25 mcg of neomycin sulfate. The vaccine and diluent contain no preservative.

a. *Recommended use.* See the generic review.

b. *Contraindications.* See the generic review.

2. *Analysis.*

a. *Efficacy.*

(1) *Animals.* No data submitted by the manufacturer. However, animal data are of minor relevance in view of the human data available.

(2) *Humans.* This vaccine was shown to produce seroconversion in 95 to 100 percent of vaccinees in the clinical trials performed to support licensure. There is considerable evidence to show that the presence of detectable HAI antibodies is correlated with protection against disease, and also a body of literature attesting to the capacity of live attenuated rubella virus vaccine to protect against attacks of the disease (see the generic review).

b. *Safety.*

(1) *Laboratory testing.* Comprehensive testing, utilizing bacteriologic media and a variety of animal species, e.g., monkeys, adult mice, sucking mice, guinea pigs, rabbits, and several cell culture host systems is done to detect the potential presence of adventitious agents and the methods employed, representing standard approaches, are acceptable.

(2) *Humans.* The safety of Cendevax rubella vaccine in man has been established through both controlled and uncontrolled clinical trials in the United States and elsewhere. Adverse reactions such as fever, rash, and lymphadenopathy have been reported but the incidence has been very low. Arthralgia appears to be the most troublesome reaction to the vaccine, especially in women. Transmission of the Cendehill strain of rubella virus through the placenta can occur. The virus has been isolated from the placenta on several occasions and, less often, from the decidua from women who have undergone therapeutic abortion following inoculation of vaccine. However, as the manufacturer points out, there has been only one instance in which rubella virus has been isolated from the fetus following maternal vaccination and this was from the femoral bone marrow and the virus was considered to have the characteristics of the Cendehill strain.

c. *Benefit/risk.* See generic review.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions—recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

(1) Gregg, N., "Further Observations on Congential Defects in Infants Following Maternal Rebella" *Transactions of the Opthal Society of Australia,* 4:119–131, 1944.

(2) Center for Disease Control, "Rubella Surveillance, January 1972—July 1973," Center for Disease Control, Atlanta, Ga., 1973.

(3) Modlin, J. F., A. D. Brandling-Bennett, J. J. Witte, C. C. Campbell and J. D. Meyers, "A Review of Five Years' Experience With Rubella Vaccine in the United States," *Pediatrics,* 55:20–29, 1975.

(4) Modlin, J. F., K. Herrman, et al., "Risk of Congential Abnormality After Inadvertant Rubella Vaccination of Pregnant Women," *The New England Journal of Medicine,* 294:972–974, 1976.

(5) Weibel, R. E., E. B. Buynak, J. Stokes, Jr., and M. R. Hilleman, "Measurement of Immunity Following Live Mumps (5 years), Measles (3 years), and Rubella (2½ years) Virus Vaccines," *Pediatrics,* 49:334–341, 1972.

(6) Weibel, R. E., E. B. Buynak, A. A. McLean, and M. R. Hilleman, "Long-term Follow-up For Immunity After Monavalent or Combined Live Measles, Mumps and Rubella Virus Vaccines," *Pediatrics,* 56:380–387, 1975.

Review of Combinations of Generically Different Vaccines

The Panel notes that those generically different viral vaccines that have been found to be safe and effective as single viral products continue to be safe and effective single-component vaccines, when combined into the products reviewed below, are found to meet the following requirements:

1. Each active component makes a contribution to the claimed effect or effects;

2. Combining of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components;

3. If administered according to adequate directions for use, and with heed to warnings against unsafe use, the combined vaccine provides a rational preventive method for a significant proportion of the target population.

The individual vaccine reviews contain information on the safety and effectiveness of each of the active components of the combination products.

No individual product review for Measles and Mumps Virus Vaccine, Live, is included here as this vaccine is not marketed in the United States. It is intended for use in those countries wher routine immunization against rubella is not recommended for young children.

Table 15, compiled by the Bureau of Biologics staff, presents data on seroconversion rates obtained with combinations of measles, mumps, and rubella virus vaccines documenting their effectiveness as antigens.

Table 15.—*Seroconversion Rates in Relation to Vaccine Titer for Combinations of Live Measles, Mumps, and Rubella*

Virus mixture and vaccine lot	Virus titer (Log 10) measles	mumps	Per human dose rubella	Seroconversion rates of double and triple negatives: Measles		Mumps		Rubella	
					Percent		Percent		Percent
Mumps and rubella:									
a		3.9	2.9			30/31	[illegible]	31/31	1.0
b		4.5	3.8			133/140	95.0	133/140	95.0
c		4.6	3.9			95/100	95.0	94/100	94.0
d		4.7	3.1			139/144	96.5	132/144	91.7
e[1]		4.2	3.5			131/138	94.9	126/138	91.3
f[1]		4.3	3.6			145/159	91.2	142/159	[illegible]
g[1]		4.4	2.8			119/122	97.5	114/122	93.4
Group		[2]4.4	[2]3.4			792/834	95.0	772/834	92.6
Totals		[3]3.9–4.7	[3]2.8–3.9						
Measles, mumps and rubella:									
h	3.4	3.7	2.8	30/30	100	[illegible]	[illegible]	[illegible]	100
i	2.8	4.4	3.6	223/237	94.1	224/237	[illegible]	[illegible]	93.7
j	2.8	4.0	4.0	209/221	94.6	207/221	[illegible]	[illegible]	[illegible]
k	3.2	4.5	3.2	222/227	97.8	220/227	[illegible]	[illegible]	92.1
Field mix	l,m,n 4.1	3.8	2.8	28/28	100	26/28	[illegible]	[illegible]	100
Group	[2]3.3	[2]4.1	[2]3.3	712/743	95.8	706/743	[illegible]	698/743	93.9
Totals	[3]2.8–4.1	[3]3.7	[3]2.8–4.0						
Measles and rubella:									
o	3.0		3.6	92/95	[illegible]			89/95	93.7
p	3.2		3.5	110/110	100			106/110	[illegible]
q	3.1		3.4	127/128	99.2			122/128	95.3
r	3.2		3.6	42/42	100			41/42	97.6
Group	[2]3.1		[2]3.5	371/375	[illegible]			338/375	95.5
Totals	[3]3.0–3.2		[3]3.4–3.6						
Measles and mumps: s	3.9	3.8		37/38	97.8	37/38	97.4		
All groups	[2]3.3	[2]4.2	[2]3.4	1120/1156	96.9	1535/1615	95.0	1828/1952	93.6
All groups	[3]2.4–4.1	[3]3.7–4.0	[3]2.8–4.0						

[1] 0.5 ml dose rather than 1.0 ml of these lots reduced virus delivered to recipient by 100.3.
[2] Mean.
[3] Range.

Measles, Mumps, and Rubella Virus Vaccine, Live ("M-M-R") and Measles and Rubella Virus Vaccine, Live (M-R-Vax) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* Each of the two products contains, in addition to its other components, further attenuated measles virus vaccine which is identical to Attenuvax. For rubella, the HPV-77 strain is used, and for mumps, the Jeryl Lynn strain is used.

2. *Analysis.*

a. *Efficacy.* The efficacy of further attenuated measles virus vaccines has been specifically tested (Ref. 1). In summary, it was found that in any combination tested of measles, mumps, and rubella, the measles component evoked serologic response in 95 percent or more of recipients, which is equal to its efficacy when given alone. Each viral component of the combined vaccine evokes a serologic response in 89 percent or more of the recipients (Ref. 1), comparable to the seroconversion rates noted when each of the vaccine components is used alone. (See also Ref. 6, p. 227.)

b. *Safety.* See generic reviews and appropriate monovalent product reviews.

c. *Benefit/risk.* The benefit/risk ratio for combinations of measles, rubella, and mumps virus vaccines or measles and rubella vaccines appears to be excellent in view of the obvious potential for such an approach in public health and mass immunization programs.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions—recommendations.* The Panel recommends that these products be placed in Category I and that the appropriate licenses be continued because there is substantial evidence of safety and effectiveness for these products.

Measles-Smallpox Vaccine, Live (Attenuvax-Smallpox) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* The vaccine contains sufficient measles virus to give a final product concentration of at least 1,000 $TCID_{50}$/dose; sufficient smallpox vaccine to give a final product concentration of at least 50,000 pfu/dose; meomycin in approximately 25 mcg/dose; and trace amounts of other antibiotics and phenol which is introduced during the processing of the smallpox component since the regulations prescribe that this combined product be bacteriologically sterile (21 CFR 630.86(a)). The label indicates that the measles virus component derives from a more attenuated strain of the Edmonston measles virus (Attenuvax) grown at low temperatures in cell cultures of chick embryo. The vaccinia virus component is prepared from calf lymph which is produced and supplied by Wyeth Laboratories, Inc. The

lyophilized product is accompanied by a vial of sterile diluent for reconstitution.

a. *Recommended use.* The labeling indicates that the combined vaccine is "recommended for single dose jet gun primary immunization of children one year of age or older against measles (rubeola) and smallpox." The recommended dose of vaccine is 0.3 ml. It is pointed out that infants less than 12 months of age may fail to respond to one or both components of the vaccine due to the presence in the circulation of residual measles and/or vaccinial antibody of maternal origin. Smallpox vaccine alone is recommended for children already immune to measles or for revaccination against smallpox.

The indicated precautions include a prohibition against giving vaccine intravenously; the necessity for burning, boiling or autoclaving the vial and stopper before disposal and sterilizing parts of jet injector; having epinephrine available for immediate use in case of an anaphylactoid reaction; admonition against giving the combined vaccine less than 1 month before or after immunization with other live virus vaccines; deferral of vaccination for 3 months following receipt of whole human blood, ISG, or human plasma; use of due caution in giving vaccine to children with a history of febrile convulsions, cerebral injury, or any other conditions in which stress due to fever should be avoided; and finally, to avoid possible false negative responses, scheduling of any contemplated tuberculin test before giving measles vaccine. Both label and package insert mention how the lyophilized vaccine should be stored and state that unused, reconstituted vaccine should be discarded after 8 hours.

Mention of fever, rash, or both occurring 5 to 12 days after vaccination or at other times during the month following vaccination, the statement that moderate fever occurs occasionally and high fever (over 103° F) less commonly; and that encephalitis and other nervous system reactions have occurred very rarely in vaccinees given the individual vaccines are included under the heading "Adverse reactions." Additionally under the same heading the label mentions thrombocytopenia, purpura, regional lymphadenopathy, febrile convulsions, conjunctivitis, headache, and mild local reactions such as erythema, induration, and tenderness. Local reactions at the site of vaccination in children who have previously received killed measles vaccine are described. A variety of systemic symptoms associated with primary vaccinia are described which may occasionally be severe and include secondary bacterial infection with enlargement of the local lesion, lymphangitis, lymphadenitis, and accessory vesicles around the vaccination site, secondary lesions due to autoinoculation, and the occasional occurrence during or shortly after the height of reaction of vacuolar or papular erythematous skin eruptions which are transient and require no treatment. Also mentioned are the more serious complications including generalized vaccinia, progressive necrotizing vaccinia, and encephalitis.

Labeling contains a section headed "Action of vaccine" which notes that fever and/or rash may develop approximately 5 to 12 days after vaccination, presumably, although not so stated, due to the measles vaccine component. The remainder of this section deals with the usual response to vaccinia virus on primary vaccination. This description conforms to the current definitions of the WHO Expert Committee on Smallpox.

b. *Contraindications.* These are given as (a) sensitivity to egg, chicken, chicken feathers, neomycin, dihydrostreptomycin, polymyxin B, sulfate or chlortetracycline; (b) active untreated tuberculosis; (c) patients receiving therapy with ACTH, corticosteroids, irradiation, alkylating agents or antimetabolites; (d) individuals with blood dyscrasias, leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic systems; (e) various gammaglobulin deficiencies; (f) individuals of any age suffering from eczema, skin conditions, wounds, or burns, or siblings or other household contacts of such individuals; (g) pregnancy; and (h) any febrile respiratory illness or other active febrile infection. No mention is made of the possible use of vaccinia immune globulin (VIG).

2. *Analysis.*

a. *Efficacy.* In the submission, items IV through VI, which deal with efficacy data, animal safety data, and human safety data are handled by reference to: (1) prior submissions for live measles virus vaccine or for combined live measles-smallpox vaccine dried; (2) license applications for Rubeovax and Attenuvax plus the supporting submissions and agenda of various dates; and (3) the license application and clinical data in support of smallpox vaccine-dried, product #72–12 Wyeth Laboratories, Incorporated. In addition, reference is made to attachments which consist of reference lists, a statement of marketing experience with Attenuvax together with summary tables of adverse reactions, and a detailed individual tabulation of serious neurologic disorders and of deaths associated with Attenuvax. The combined product has not been marketed in this country.

b. *Safety.* See above.

c. *Benefit/risk.* This product is a combination of two generically distinct live virus vaccines, which is for administration only by automatic jet injection for primary vaccination against smallpox and simultaneous immunization against measles. Its use is therefore currently limited to those areas of the world where simultaneous measles and smallpox immunization is a routine practice. Both vaccines are well established as effective individually, but they differ with respect to safety. In the case of the vaccinia component, the degree of risk in this country is currently judged to outweigh the potential benefit. In areas of the world where smallpox is, or has recently been endemic, vaccination is a significant benefit. With respect to the measles component, the risk is extremely small and is far outweighed by the benefits provided by protection against the naturally occurring disease.

d. *Labeling.* In the contraindications section of the labeling, the prohibition against vaccination in the presence of febrile respiratory illness or other active infection might be modified by the reasonable provision, "Unless contracting measles or smallpox involves greater risk." The list of contraindications is relatively complete, but the portion dealing with eczema and other skin conditions with special reference to household contacts of persons so afflicted should be in boldfact type or otherwise given special prominence. Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions—recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Rubella and Mumps Virus Vaccine, Live (Biavax) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This is a combination of mumps virus vaccine, live (Mumpsvax) and of rubella virus vaccine, live (Meruvax) (see the descriptions given in reviews of these two vaccines). Each dose of this combined vaccine contains not less than 5,000 $TCID_{50}$ of the Jeryl Lynn strain of

mumps virus (grown in chick cell tissue culture) and not less than 1,000 $TCID_{50}$ of the HPV–77 strain of rubella virus (grown in duck cell tissue culture). Each dose also contains 50 mcg of neomycin.

a. *Recommended use.* This product is designed to permit simultaneous immunization of children, age 1 to puberty, against rubella and mumps.

b. *Contraindications.* These are listed as pregnancy or prospect of pregnancy within 3 months; sensitivity to vaccine components, viz, chick or duck egg proteins or feathers, or neomycin; any febrile illness; blood dyscrasis (leukemia, lymphoma, generalized malignancies); and altered resistance from therapy (ACTH, corticosteroid, irradiation, alkylating agents, and antimetabolites).

2. *Anaylsis.* a. *Efficacy.*

(1) *Animals.* Not applicable.

(2) *Humans.* Four lots were administered to 415 children, 7 months to 7 years of age, who were initially without antibody against either mumps or rubella virus. Overall, 94.7 percent developed rubella hemagglutination inhibiting antibodies and 96 percent developed mumps neutralizing antibodies. The antibody responses elicited approximated those induced by either vaccine component given alone, and the pattern of antibody persistence, as measured at 2 years postvaccination was the same as that observed with the monovalent vaccines.

The combined vaccine is presumed to have the protective effectiveness equivalent to that provided by the monovalent vaccines.

b. *Safety.*

(1) *Animals.* The vaccine passed all the required safety tests.

(2) *Humans.* Clinical reactions, including joint involvement and fever, were notably absent among the children during the 28-day follow-up.

c. *Benefit/risk.* The ratio is good; vaccine associated reactions are assumed to occur at the same rate as those observed following the use of monovalent vaccine components.

d. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

3. *Conclusions—recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Reference

(1) J. J. Witte, "Simultaneous Administration of Live or Killed Vaccines," *in* "Symposia Series in Immunobiological Standardization," Vol. 22, Edited by F. T. Perkins, S. Karger, London, pp. 163–171, 1973.

Generic Review of Influenza Vaccines

Background

Unlike smallpox and poliomyelitis, influenza continues to plague man with periodic outbreaks of variable severity. Pandemics, affecting hundreds of millions of persons, may still be expected to occur.

Technologic advances have been contravened by biologic factors which are peculiar to influenza; foremost among these are the genetic instability of the causal viruses, which results in frequent major antigenic changes, and the short-lived immune responses which follow the natural disease as well as vaccination.

Nevertheless, vaccines prepared with virus strains responsible for current influenza have resulted in a significant reduction of cases of disease. A review of the benefit-risk factors clearly indicates that influenza vaccine has prevented thousands of cases of influenza, with most of the well-controlled trials having been conducted in young adults. It is believed that mass use of influenza vaccine will prevent a significant number of deaths, especially in high-risk groups.

Influenza virus vaccine is prepared from the extra-embryonic fluids of influenza virus-infected chick embryos. Whole virus is separated from nonviral egg proteins and debris by several purification steps, and concentrated by density gradient centrifugation and/or ultrafiltration. The virus is inactivated by formaldehyde and suspended in a sodium chloride solution with various buffers. These monovalent aqueous suspensions are titrated, adjusted to give the chick cell agglutination (CCA) unit content desired prior to combination, and pooled with the appropriate A or B strains in proper proportions to give the required CCA unitage per dose. Some producers employ viral disruption procedures utilizing polysorbate and ethyl ether or tri-n-butyl phosphate to prepare "subunit" vaccines.

In interpandemic years the ACIP policy emphasizes prevention of the most serious effect of the disease, i.e., excess mortality, by routine, annual immunization of individuals at high risk. The high-risk population is comprised of persons aged 65 and over, plus younger persons affected with chronic diseases, especially cardiopulmonary, which are believed to heighten vulnerability to a fatal outcome of influenzal infection.

Other groups on which special attention is focused are children and persons in essential positions, such as hospital employees or military personnel. Arguments have been advanced in support of the strategy of immunizing children, especially school children in order to limit, through herd immunity, the spread of the virus. While current interpandemic year recommendations do not emphasize this approach, vaccine formulations and dosage schedules should allow for such usage in the future.

Current evidence indicates that protection against the homologous virus strain persists for at least 1 year and in one study as many as 3 years. However, the present recommendation is for annual vaccination of high-risk groups.

Both monovalent and multivalent vaccines have been used in the past. The 1973 to 1974 formulation, which was submitted for review, was a bivalent one, with unequal amounts of influenza A (700 CCA) and B (300 CCA) viruses. Just how much total antigen should be included in a single dose is still the subject of debate. Experience accumulated during the clinical trials conducted in support of the National Immunization Program of 1976, suggests that the proper dose depends on the previous influenza experience of the vaccinee. (See Addendum following this section.)

Route of immunization has been another topic of debate. Intradermal injection appears to be inferior to either intramuscular or subcutaneous vaccination. While immunization by jet injection induces a high rate of local reactions, these are not of sufficient import to preclude the use of jet injection in mass immunization campaigns, and the resultant antibody responses are equivalent to those induced by intramuscular or subcutaneous vaccination. Intranasal immunization is still considered experimental.

None of the presently available influenza vaccines contains alum or other adjuvants. One product, the ether-tween split vaccine of Parke, Davis & Co. at one time contained aluminum phosphate; this was subsequently deleted from the vaccine when evidence was adduced that the aqueous vaccine was adequate in itself to stimulate antibody formation in adults.

Contraindications are given as follows:

1. The presence of acute respiratory or other active infections.

2. A history of hypersensitivity to chicken, chicken feathers, egg or egg products.

Analysis

1. *Efficacy.*

a. *Animals.* Many studies in animals, particularly the mouse and ferret, have demonstrated that killed virus vaccines protect against challenge with homotypic live viruses. The antibodies directed against the viral hemagglutinin neutralize infectivity and are responsible for protection against infection. The antibodies against the neuraminidase are believed to inhibit multicycle viral replication and spread of infection within the host and may serve to modify disease if infection does occur. Such models, adapted to the measurement of vaccine immunogencity, can provide basic information useful to the regulatory field. However, no animal model so far developed yields data which correlate consistently with observations in man.

b. *Human.* Inactivated, aqueous, whole virus influenza vaccines of adequate potency have been shown to provide substantial protection during epidemics caused by virus strains identical to or closely related to those contained in the vaccine. More data in support of this statement are available from well-controlled field trials for the Type A virus vaccines than for B vaccines, since the efficacy of the B component in any of the currently formulated vaccines has not been proven. Only a few well-controlled trials have involved the high-risk populations for which the vaccine is particularly recommended.

The protective efficacy of commercially prepared subunit vaccines is not clearly demonstrated. The problem is a two-part one. First is the question whether HI antibody induced by subunit vaccine is as preventive of disease as antibody induced by either whole virus vaccines or natural infection. This question, which is addressed in detail in the product reviews, has been only partially resolved in controlled vaccine, trials; the evidence from experimental animal models and inconclusive trials in humans favors the view that protective of vaccinees is correlated with the level of postvaccination HI antibody without regard to the type of vaccine administered.

The second issue is the capacity of subunit vaccines to stimulate antibody in human subjects. The preponderance of evidence from comparative studies of H_3N_2 subunit and whole virus vaccines suggests that subunit products are equally antigenic in adults but less antigenic in children. Results from 1976 trials of vaccines containing antigens in the A/Swine family indicate clearly that young recipients (those 3 to 10 years old) respond poorly to a single injection of subunit vaccine, when whole virus vaccines at the same or lesser dosage (in CCA units) often stimulate measurable HI antibody. It is likely that the poor response of children, especially to subunit vaccine reflects a lack of prior experience with related antigens. This is supported by the fact that older individuals (over 24 years) respond as well to subunit as whole virus vaccines. It is probable that the satisfactory response of seronegative school-age children and young adults to H_3N_2 subunit vaccines reflects prior experience with the same or related antigens, despite the absense of detectrable homologous HI antibody.

Efficacy data for vaccines prepared by current production methods are provided in the section on Reviews of Individual Influenza Virus Vaccine Products.

In the case of influenza, there are two compelling factors which lead to changes in vaccine formulation. First, the manufacturer regularly changes the component strains as directed by the PHS to conform with shifts in the antigenic makeup of epidemic strains. Evidence of the protective efficacy of current formulation is therefore difficult or impossible to obtain before the vaccine must be released for use. This poses special problems which are addressed under the heading Recommendations below. Second, the manufacturer may change the basic production process as acquisition of basic information and technical knowledge makes a superior or more economic product possible.

Nevertheless, the accumulation of certain data is desirable. For example, this information includes the history of the virus strain or strains to be used, as well as subsequent passage history and evidence of consistency in quality.

2. *Safety.* Local and systemic reactions to influenza vaccines do occur. The most commonly reported reactions are soreness, redness, and swelling at the site of injection and fever, malaise, and headache during the 24 hours following vaccination. These reactions may be briefly disabling and have been reported, on an episodic basis, with undesirable frequency. Such reactions have adversely influenced vaccine acceptance. While there is evidence to support claims that purified whole virus or subunit vaccine as currently produced are less reactogenic than earlier, conventional vaccines, this is now a less relevant factor in recommending one vaccine over another, inasmuch as no licensed products are any longer conventional. However, while major systemic reactions are now rarely reported, there is evidence that, at least in children, subunit vaccines are appreciably less reactogenic than whole virus products.

Febrile reactions are more common in children than in adults. These, as well as other systemic reactions, are in part related to preexisting immunity. Thus, there is an inverse correlation between incidence of systemic reactions and HI antibody against the vaccine strain or history of a recent homologous immunization. In children under 3 years of age, administration of large (adult) doses of whole virus vaccine has been associated with a rapid rise in temperature 6 to 9 hours later and, in a few instances, convulsions. Dosages in this age group which are both immunogenic and of acceptable reactogenicity remain to be established.

Information has accumulated recently on the extraneous, nonviral content of influenza vaccines. The stimulus for this data gathering has been the limited understanding of the factors underlying the variable systemic reactogenicity of the more purified present-day vaccines, and the lethality of some recent formulations for guinea pigs after parenteral injection (done as part of the routine, final safety test). This lethal effect for guinea pigs has been attributed to both the endotoxin and the viral content of the vaccine. Vaccine lots containing less than 0.8 microgram/milliliter (mcg/ml) of endotoxin have not killed guinea pigs, and those containing more were lethal in proportion to the amount of endotoxin present. Endotoxin alone, however, is not entirely responsible.

In the process of these investigations, information was also obtained on the content of diffusable egg protein, total protein, residual formalin, and particulate contaminants visible by electron microscopy. The characteristics (contaminating diffusable chick protein, endotoxin, total protein, and formalin content) of six recent influenza vaccine lots in this respect, as determined by the Bureau of Biologics, are illustrated in Table 16.

Table 16.—*Chemical and Biological Characteristics of Six Lots of Bivalent Influenza Vaccine*

Manufacturer	Vaccine Type	Vaccine CCA	Total protein [1]	Chick cell protein [1]	Limulus endotoxin [1]	Rabbit pyrogen [2]	Formalin
A	ZPWV	[illegible]	239	0.5	0.06	UNDIL.	[illegible]
B	ZPWV	1150	442	0.5	[illegible]	1.10	[illegible]
C	ZPWV	1440	243	<.01	<.001	0	[illegible]
D	CPWV	1050	1480	[illegible]	[illegible]	1.100	4.4
E	TBP	1120	206	10.55	0.02	1.10	[illegible]
F	ET	1240	114	<.01	0.11	0	6.2

[1] Microgram/dose.
[2] Last dilution which induced a mean temperature elevation of >.5° C.

Key.—ZPWV: Zonally purified whole virus.; CPWV: Chromatograph purified whole virus; TBP: Tri-batyl phosphate; ET: Ether treated.

The reactogenicity and antigenicity of these six vaccines were carefully compared by the Bureau of Biologics and a recent clinical trial. There was no demonstrable association of any contaminant or combination of contaminants with adverse systemic reactions. Further studies which compared vaccines with widely differing endotoxin concentration have confirmed this conclusion. Nevertheless, since endotoxin was considered undesirable in itself, the Bureau of Biologics took steps in the fall of 1974 to limit the permissible content in the following year's vaccines. At the same time, the guinea pig safety test was altered by the stipulation that the vaccine may be inoculated subcutaneously to avoid deaths believed more attributable to inherent properties of the viral antigens than to adventitious toxic compnents.

The extensive experience in the clinical trials of "swine influenza" vaccines in 1976 corroborated these conclusions. Endotoxin content was not related to systemic reactogenicity. Rather, it was clear that split virus vaccines were of low reactogenicity and that the toxicity of whole virus vaccine was related to the viral mass then contained. An additional risk of influenza vaccination became evident in the National Immunization Program in the fall of 1976, namely the excess occurrence of Guillain-Barre-Syndrome (GBS) in persons who had recently received vaccine.

3. *Benefit/risk.* Epidemic influenza is associated with a considerable morbidity and, in certain groups, an excess mortality. Prevention of such disease and death is highly desirable. The risk associated with present vaccines is small, even including the risk of GBS. (See Addendum following this section.) Their efficacy, when they are properly matched against the infecting strains, is between 60 and 90 percent. Thus, the benefit-risk ratio is, from the data available, acceptable. There is, however, a compelling need for efficacy studies in high risk populations so that the true benefit/risk ratio in these target groups can be more precisely assessed.

4. *Labeling.* Labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP.

Recommendations

Since influenza vaccines must, of necessity, be produced with continuous changes in formulation, a review of effectiveness prior to release of a current lot must focus more on the process of manufacture than on specific viral strains. Assumptions regarding a given process must be based on knowledge of safety, antigenicity, and effectiveness of vaccines produced by that process. In addition, recently acquired information on vaccine contaminants raises a number of questions which cannot be answered at this time.

1. *Potency of licensed vaccines.* The present method for standardizing vaccine potency (by CCA units) does not take into account fragmentation and aggregation of viral particles and other possible factors which are clearly of importance in determining the antigenicity and reactogenicity of a vaccine in man. For this reason, the Bureau of Biologics should be encouraged to continue its investigations on the possible supplementary use, or even substitution, of other tests of potency, in particular, suitable animal test models and in vitro measurement for antigenic mass. (See Addendum following this section.)

2. *Presence of nonviral components.* The Bureau of Biologics should establish standards of the maximal acceptable level of nonviral components in influenza vaccines. Regulations cover the endotoxin content, and if adequate quantitative measurements can be developed, the content of nonviral protein and of diffusible chick protein should be similarly covered by regulations.

In addition, efforts should continue by the Bureau of Biologics, National Institutes of Allergy and Infectious Diseases (NIAID), and the Center for Disease Control (CDC) to determine what components of present-day vaccines are responsible for local and systemic reactions in man. An important aspect of such efforts would be prospective studies of representative recipients of a suitable number of consecutive vaccine lots to identify the most reactogenic lots for further study and to determine the reason for the lesser reactogenicity of split-virus vaccines.

3. *Vaccine antigenicity, safety, and efficacy.* It is a characteristic of influenza vaccines that component virus strains need to be changed frequently. It is also probable that manufacturers will from time to time introduce changes in the manufacturing process. Control of the vaccines for changes in the component viral strains and in the manufacturing process is the responsibility of the Bureau of Biologics. The extent and nature of testing in vitro, and in animals and man, necessary with each change to demonstrate the safety and potency of each new vaccine should be, as far as possible, prescribed in detail. The following guidelines are submitted by the Panel to aid the Bureau in its delineation of rules and regulations.

A major change in process is defined as (1) one which alters the nature of the virus so that whole particles are no longer the major antigenic units; (2) one which changes the ratio of the mass of component virus parts (such as hemagglutinin, neuraminidase, etc.) to each other; (3) one which introduces major extraneous components into the vaccine (such as adjuvants, detergents, etc.); or (4) any other change which the Bureau deems is sufficiently significant to require extensive proof of safety and efficacy. A change of this nature will necessitate carefully controlled tests of safety and antigenicity in adults and children. The new product also should be shown to be comparable or superior to vaccines prepared by acceptable earlier processes. In addition, evidence should be presented that a well-designed trial of the efficacy of the vaccine in man is in process. The trial should be expected to provide data concerning the efficacy of at least one of the several antigenic components. The requirements concerning major changes should be enforced retroactively, if the requirements have not been satisfied in relation to a prior major change. In this regard, currently available whole virus vaccines are similar enough to one another that trials of protective efficacy (but not of antigenicity or of safety) carried out with one such vaccine may be considered to apply to all whole-virus vaccines of similar or greater

potency as established by appropriate laboratory testing.

Minor changes in manufacturing process which would not reasonably be expected to alter either the safety or antigenicity, would necessitate lesser amounts of safety and antigenicity testing, confined to adults. Such requirements would likewise be enforced retroactively, if necessary, for prior minor changes.

Changes in component virus strains, dictated by the Bureau, do not require efficacy tests for protective effect of each vaccine in human subjects. However, particularly in view of the recent experience with A/Swine vaccine, new strains ideally should receive antigenicity testing in a small number of human subjects of a suitably wide age range so that there is assurance of potency in the age groups for which the vaccine is recommended. Antigens of new strains should also be investigated for their immunogenicity, i.e., ability to induce protective immunity, in animal models. Perhaps the Bureau may find it of advantage to have each manufacturer conduct animal immunogenicity trials with his own vaccine and compare it in potency with a standard vaccine.

4. *Special studies.* There are a number of other issues which the Panel believes should be examined by the Bureau, in collaboration with NIAID, CDC, and the ACIP.

a. Vaccine trials in high-risk adult groups are needed, since, although these are the priority target populations, information on efficacy is scanty. The construction of placebo or unvaccinated control groups must take into account the fact that vaccine is recommended in such individuals; hence, only persons refusing offered vaccine would be eligible as controls.

b. Studies should be undertaken of the safey, antigenicity, and protective effect of vaccines in children under 6 years including, in particular, those with no prior influenza infection experience. The problems of dose, vaccination schedule, and toxicity require special investigation. Monovalent vaccines will be required to examine differences in toxicity of Type A and Type B viral components. On epidemiological grounds, prevention of infection among young children would be desirable. Further, the ability to immunize effectively and safely those who have never experienced influenza infection may be of greater importance when the next major antigenic variant emerges and a much larger proportion of the population will fall into this category. As noted in previous sections, in the young age group the advantage lies with subunit vaccines for reactogenicity but with the whole virus product for immunogenicity. The Panel believes resolution of this dilemma is of critical importance. As noted in the Addendum (following this section), the results of the 1976 nationwide clinical trials have provided one solution to this problem, i.e., a two-dose regimen of subunit vaccine.

c. Particularly emphasis should be placed on investigating the protective efficacy of the B component in current vaccines. Although B vaccines have been shown to induce sufficient protection in both civilian and military populations, these formulations contained less antigen than presently recommended, sometimes with an adjuvant. In comparison with A vaccines, B vaccine field trials have been few in number, a fact attributable to the different epidemiology of B infections (Ref. 13). Further, data from one study suggests that natural infection with Type B affords negligible protection against reinfection and associated disease. In addition to well-controlled field trials, consideration needs to be given to volunteer challenge studies to support continued inclusion of B virus, and its amount, in future vaccines.

D. The bureau should periodically review the status of adsorbants and adjuvants in experimental influenza vaccnes, as more data are collected on their safety and efficacy in human subjects.

e. Recent experience with swine influenza vaccines underlines the importance of rare but severe vaccination sequellae. In this particular case, the disease was GBS, but other diseases may also occur with other latent periods and enter into the calculation of benefit-risk ratios. The Bureau, in cooperation with CDC and NIAID, should remain on the outlook for such rare events, following influenza and other vaccines, both live and inactivated. These problems are discussed more fully in the Introductory comments section of this document.

Addendum to Generic Review of Influenza Virus Vaccines

The foregoing review was essentially completed in late 1975 and modified slightly in June 1976 in light of the early results of the nationwide clinical trials of influenza vaccines, sponsored by NIAID in relation to the National Influenza Immunization Program. On January 20, and 21, 1977, the many investigators participating in these trials made formal presentations of their data at a meeting at National Institutes of Health (NIH) in Bethesda. The more than 50 separate presentations and, presumably, the related discussions are to be published in a special supplement of "The Journal of Infectious Diseases." At the same meeting the significant data relating to the possible association between influenza vaccination and GBS were presented by a representative of CDC. The following is a summary of the most important findings and conclusions resulting from the clinical trails and of the problem posed by GBS. Their documentation can be found in "The Journal of Infestious Diseases" supplement and/or (for GBS) contemporary issues of the "Morbidity and Mortality Weekly Report."

The clinical trials had as their objective determination of the dose (or doses) of monovalent (A/Swine) and bivalent (A/Swine plus A/Victoria) influenza vaccines produced by four manufacturers which would induce satisfactory immune response with an acceptably low level of reactions. These trials involved nearly 8,000 volunteers ranging in age from 6 months of 65 years and older and were conducted by over 20 teams of investigators, all of whom followed a common basic protocol. This protocol called for inoculation of healthy or high-risk volunteers in prescribed age groups with randomly assigned, coded preparations, each representing a particular dose of vaccine produced by one of the four manufacturers or an inert placebo. Also required was completion of careful records concerning local and systemic reactions during the 48 hours postinoculation and collection of appropriate blood specimens to determine antibody response. All antibody assays were done—still under code—in the laboratories of CDC.

Reactions to vaccines were related to type and dose of vaccine, the method of inoculation, and the age and immune status of the vaccinees. Method of inoculation (intramuscularly, by needle, or jetgun) was related only to local reactions; these were more common and somewhat more extensive when the jetgun was used. Whole virus vaccines tended to induce more frequent and more serve systemic reactions (fever, headache, malaise, etc.) than did split virus or subunit vaccines. Moreover, there was no evidence that, in persons 3 years of age and older, subunit vaccines had any significant systematic toxicity in the dosage levels tested. The incidence and intensity of systemic reactions with a particular whole virus vaccine tended to increase with vaccine dose especially in the younger age groups. A history of a recent previous homologous vaccine injection or a level of preexisting vaccine-strain specific HI

antibody appeared to mitigate reactivity. Within the range of vaccines tested no other factor, e.g., endotoxin content, was related to reactions. The inescapable conclusion is that the principal cause of immediate systemic reactions is something within the virus itself, which is largely lost or masked during the manufacture of split virus vaccines and which is obstructed by viral antibody.

Immune response (measured by HI antibody titer) also was related to type and dose of vaccine and to age vaccinee. For persons 25 years and older, the smallest single doses tested (200 CCA) of vaccines produced by each manufacturer (two whole virus, two split virus) induced acceptable responses to both A/Swine and A/Victoria antigens. In younger individuals, the results were different, especially for response to the A/Swine antigen. Response to whole virus vaccines tended to exceed that to subunit vaccines but no dose tested, even of the more potent whole virus vaccine, induced satisfactory response (HI titer of 1:40 or higher) in seronegative volunteers with acceptable frequency. This outcome suggested that the prior infection experience of persons 25 years and older, i.e., experience with influenza A strains prevalent prior to 1957, had conditioned or primed them immunologically to respond anamnestically to the A/Swine antigen. An obvious general conclusion is that the dose of any specific vaccine needed to induce satisfactory immune response is in large part dependent on the previous influenza antigen experience of the vaccinees.

The relative failure of vaccines in younger person meant that futher trials were necessary. The frequency of systemic reactions to the largest doses of whole virus vaccines tested was unacceptably high, especially in those under 18 years of age. This made it clear that simply increasing the dose of vaccine was not the answer and led to trails of regimens involving two doses of vaccine. The importnat outcome of these trials was that subunit vaccines, in adult doses (200 CCA of monovalent A/Swine or bivalent with 200 CCA of each antigen) proved nonreactogenic and satisfactorily immunogenic in ages as young as 3 years. Trials in still younger children (down to 6 months) were conducted in too few subjects to justify firm conclusions, but the results suggested that, in reduced dose (100 CCA), the two-dose regimen of subunit vaccine also may be successful. Two small doses of whole virus vaccines, while still reactogenic, also proved highly immunogenic. Thus, it appears that influenza vaccine can be used effectively and safely in young children if a two-dose regimen of subunit (and possibly even of whole virus) vaccine is employed. Such a regimen, although not ideal, would be acceptable in the interpandemic period. However, in the face of a threatened pandemic posed by a major influenza A variant, time would be a critical factor and a one-dose vaccination would be highly desirable.

A possible way to achieve this is suggested by studies with highly purified preparations of hemagglutinin and neuraminidase. Although these proved poorly immunogenic alone, combining these with small amounts of whole virus greatly enhanced their immunogenicity. This suggests that a similar addition of small amounts of whole virus to standard subunit vaccines might have a similar enhancing effect.

A further important byproduct of the trials was the result of efforts to quantitate the hemagglutinins and neuraminidase content of vaccines. Methods of measuring hemagglutinin content of vaccines, based on immunodiffusion in antibody-containing agar, show great promise as prospective regulatory tools which may substitute for the CCA test (Ref. 1). In the trials, hemagglutinin levels, although still not precisely predictive, correlated better than CCA content with both the reactogenicity of whole virus vaccines and the antigenicity of all vaccines in some age groups. The methods for neuraminidase measurement are still in development and further research should be encouraged.

The National Immunization Program was initiated effectively as of October 1, 1976. By mid-December some 45 million doses of vaccine, monovalent A/Swine or bivalent A/Swine plus A/Victoria, had been given, almost exclusively to adults (18 years and older). Use in younger persons (other than high-risk) was effectively prevented by lack of the recommended subunit type of monovalent vaccine. As of December 16, 1976 a moratorium on the further use of influenza vaccine was declared because of a possible association between vaccination and occurrence of GBS. As of January 12, 1977, 582 cases had been recognized in the United States with onsets on or after October 1, 1976, nearly 300 of which had received influenza vaccine within 4 weeks prior to onset. Analysis of the available information, including age distribution and age-specific rates, suggests that vaccination was associated with a 10-fold increase in the risk of developing GBS within the month following vaccination. (This increase in risk is estimated at 1 in 110,000 vaccinations.)

The fundamental cause of GBS remains unknown. A widely accepted hypothesis is that it is a form of autoimmune disease which may be triggered in peculiarly vulnerable persons by immune response. Prior reviews implicate naturally occurring acute infections of many types as the most common triggers. The experience in fall, 1976, makes it clear that vaccination, at least influenza vaccination, also can serve as a trigger. Thus, in describing the possible risks associated with influenza vaccine, GBS must be included. This risk of developing the syndrome is estimated at one in 110,000 vaccinations. Although most cases of GBS recover fully, respiratory paralysis results in death in about 3.5 percent of cases. This is an extremely small risk which is far outweighed by the potential benefits of successful immunization.

Reviews of Individual Influenza Virus Vaccine Products

Influenza Virus Vaccine, Bivalent (Flu-Immune) Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* The package circular states that:

Influenza Virus Vaccine, Bivalent Flu-Immune, Lederle is prepared from the allantoic fluid of embryonated chicken eggs infected with influenza virus. The virus is inactivated with formaldehyde and ethylene oxide. The concentrated virus is suspended in a buffered diluent containing sodium citrate, sodium phosphate monobasic and sodium phosphate dibasic. Thimerosal (1:10,000) is added as a preservative and the preparation is further purified by a chromatographic process.

In chromatographic purification the conventionally prepared Influenza Virus Vaccine is passed through a molecular sieve composed of chemically inert, porous, borosilicate spheres. These spheres have controlled size pores which entrap extraneous protein.

Chromatographically purified Influenza Virus Vaccine has significantly less extreneous protein content than conventionally prepared Influenza Virus Vaccine, as measured by protein determinations and electron micrographs. . . .

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.*

a. *Efficacy.*

(1) *Animals.* Potency data were not submitted.

(2) *Humans.* Data have been submitted on an antigenicity study which may be summarized as follows:

(i) *Investigator.* Peninsular Testing Corporation, North Miami, FL (Annual Progress Report, September 1973).

(ii) *Vaccine.* Flu-Immune-Bivalent. Each 0.5 ml dose contains:

A2/Aichi/2/68–X–31—700 CCA units.
B/Mass/1/71—300 CCA units

(iii) *Population:* Adult volunteers, 17–69 years.

(iv) *Dosage.* Group I—0.5 ml intramuscularly (100 subjects); Group II—0.5 ml subcutaneously (100 subjects); Group III—two 0.5 ml doses, intramuscularly, 6 weeks apart (46 subjects); Group IV—two 0.5 ml doses, subcutaneously 6 weeks apart (43 subjects).

(v) *Results.* Two 0.5 cc vaccine doses spaced 6 weeks apart stimulated a fourfold increase in HI antibody titer in approximately 70 percent of individuals given the vaccine intramuscularly and approximately 64 percent of those given the vaccine subcutaneously. Details of the serologic responses are presented in Tables 17 and 17a.

Table 17.—*Summary of Results Obtained in Antigenicity Study of Flu-Immune, Bivalent*

Vaccine group	Geometric mean titers					
	MASS-B			X-31		
	Preinoculation	6 weeks	12 weeks	Preinoculation	6 weeks	12 weeks
Intramuscular, 1 dose	17.7	141.4	103.1	23.7	214.4	130.6
Intramuscular, 2 doses	18.6	95.5	102.4	25.0	185.4	201.6
Intramuscular, all	18.1	115.7	102.7	24.3	199.0	163.9
Subcutaneous, 1 dose	20.3	[illegible]	[illegible]	27.8	138.8	138.8
Subcutaneous, 2 doses	17.9	108.7	[illegible]	23.1	128.6	129.8
Subcutaneous, all	19.0	95.4	[illegible]	25.4	148.1	134.0
Combined	18.5	105.4	95.5	24.8	167.0	148.5

Table 17a.—*Summary of Results Obtained in Antigenicity Study of Flu-Immune, Bivalent—Individuals Showing a Fourfold Rise in Titer*

Vaccine group	MASS-B		X-31	
	6 weeks	12 weeks	6 weeks	12 weeks
Intramuscular, 1 dose	30/45 (67%)	28/41 (68%)	32/45 (71%)	23/41 (56%)
Intramuscular, 2 doses	30/47 (64%)	34/45 (76%)	30/47 (64%)	34/45 (76%)
Intramuscular, all	60/92 (65%)	62/86 (72%)	62/92 (67%)	57/86 (66%)
Subcutaneous, 1 dose	30/44 (68%)	27/39 (69%)	32/44 (73%)	23/39 (59%)
Subcutaneous, 2 doses	28/43 (65%)	26/43 (60%)	25/43 (58%)	29/43 (67%)
Subcutaneous, all	58/87 (67%)	53/82 (65%)	57/87 (66%)	52/82 (63%)
Combined	118/179 (66%)	115/168 (68%)	119/179 (66%)	109/168 (65%)

It is assumed that vaccines of this antigenicity will induce a significant degree of protection. However, no studies are mentioned in the submission nor were any found in the recent literature which demonstrate the protective efficacy of Lederle Laboratories vaccine as last prepared. One study employed a Lederle Laboratories vaccine presumably prepared by older methods and demonstrated a protective effect (Ref. 2). Likewise, the X–31 recombinant vaccine described by Kilbourne has been shown to be effective in volunteer challenge experiments.

b. *Safety.* (1) *Animals.* See generic statement. Data on COFAL testing were not given in the producers submission.

(2) *Humans.* In the study cited above, "there were no significant differences (subcutaneous vs intramuscular) in the local or systemic reactivity immediately following vaccine administration. However, there were statistically significant differences observed in the local reactivity at 24 hours post-inoculation. Individuals who were administered vaccine intramuscularly had fewer incidences of erythema (8/95) and induration than the subjects who received the vaccine by subcutaneous administration (34/93)." There were no significant differences in systemic reactivity (e.g., chills=4/95 vs 3/93).

The producer has received 35 written complaints for the many millions of doses marketed.

c. *Benefit/risk.* See generic review.

d. *Labeling.* See generic review.

3. *Conclusions—Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license be continued because there is substantial evidence of safety and effectiveness for this product.

Influenza Virus Vaccine, Bivalent (Zonomune) Manufactured by Eli Lilly & Co.

1. *Description.* The package circular states:

Influenza Virus Vaccine, Bivalent, U.S.P., Zonomune(R) (zonal centrifuged vaccine, Lilly) is composed of the recommended contemporary strains of influenza viruses. The vaccine virus is grown in embryonated chicken eggs but is not processed by the usual differential centrifugation technics. Instead, the virus is purified and concentrated in a sucrose density-gradient solution by means of a continuous-flow isopycnic centrifugation process. By this procedure, the virus can be removed selectively from the nonviral components of the egg fluid. Amorphous and cellular residue usually found in conventionally produced vaccine (as demonstrated by electron micrographs) is discarded. Furthermore, laboratory studies utilizing gel-diffusion technics have demonstrated a significant reduction in specific soluble chicken-protein components in vaccine manufactured by the Zonomune process as compared with conventionally produced vaccine. As a result of these new production methods, the adult dosage volume has been decreased by half, to 0.5 ml., while retaining full antigenic potency * * *.

* * * Neomyucin has been added to the virus inoculum, and negligible amounts remain after processing. The virus is inactivated with formaldehyde solution (no more than 1:10,000 in the final product) and preserved with Merthiolate(R) (thimerosal, Lilly), 1:10,000. Iodoacetic acid was used as a preservative during the processing and does not exceed 0.15 mcg./ml. in the final vaccine. The preparation also contains Gelatin, U.S.P., 0.2 percent, and sucrose, less than 10 percent, in the final product.

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.* a. *Efficacy.*

(1) *Animals.* See generic statement.

(2) *Humans.* Since Zonomune manufactured by Eli Lilly & Co. was the first zonal centrifuge purified vaccine available, it was extensively tested during the 1968 to 1969 Hong Kong influenza epidemic. There are several studies showing that immunization at that time conferred protection both in adults and in children.

(i) *Antigenicity.* Data adduced in 1967 are provided comparing human reactivity to vaccine (containing Taiwan and Maryland B strains) produced by isopycnic and by Sharples centrifugation. On the basis of

equivalent populations in regard to prior immunization status, four lots of isopycnic vaccine produced a rise in HI antibody titer equivalent to that found in Sharples vaccine.

(ii) *Protection.* The following studies have been excerpted from the literature:

(*a*) *Study I.*

Investigator. Knight et al. (Ref. 3).

Vaccine. A_2/Aichi/2/68 Monovalent. Prepared by continuous flow zonal ultracentrifugation; formol inactivated.

Population. Prisoners, November 1968.

Challenge. Natural epidemic caused by Hong Kong virus strains.

Results. Conclusion based on occurrence of illness in relation to dose. (See Table 18).

There was significantly less illness (5.6 percent) among men who received the three higher doses of vaccine than among nonimmunized men (11.7 percent) ($X^2=5.46$; $P<0.03$). When only febrile cases were considered, the difference between the occurrence of illness among all immunized and nonimmunized men was significant ($X^2=4.46$; $P<0.05$), with even greater differences for higher doses.

Table 18.—*Illness in Vaccinated Volunteers Exposed to Natural Challenge*

Dose of vaccine CCA units	Number vaccinated	Acute respiratory illness	
		Febrile	Afebrile (>99°F)
1265	78	3	1
535	39	1	3
332	59	2	1
137	60	7	2
54	14	2	1
Immunized group	270	15	8
No vaccine	755	76	12

(b) *Study II.*

Investigator. Gwaltney et al. (Ref. 4).

Population. Elderly psychiatric patients, November 1968.

Vaccine. (*1*) Zonomune, monovalent A_2 (400 CCA Hong Kong virus in 0.5 ml); (*2*) Control-B/Mass/3/66 (Lilly), 400 CCA units in 0.5 ml; (*3*) Booster Vaccine (Lilly) 1965–70 bivalent formulation.

Dosage. (*1*) Jet injector, 0.5 ml, 400 CCA A_2/HK; (*2*) Jet injector (control) 0.5 ml, 400 CCA, B/Mass; (*3*) Spray: 0.125 cc (100 CCA) nebulized into each nostril and 0.25 cc (200 CCA) into orophraynx during inspiration. The groups are described in Tables 19 and 20.

Results. There was a significant reduction in the influenza attack rate in the group receiving vaccine by jet gun (5.5 percent) or by gun spray combined (5.4 percent) as compared to the controls (14.7 percent) or those receiving vaccine by spray alone (12.2 percent).

(c) *Study III.*

Investigator. Couch et al. (Ref. 5).

Vaccine. A_2/Aichi/2/68; 503 CCA units/ml; 1.0 ml given intra-muscularly. (This vaccine was compared with the A_2/X–31 vaccine (556 CCA units/ml), which is not made by Eli Lilly and Co.)

Population. Adult volunteers (prisoners).

Challenger. A_2/Aichi live virus; first passage HEK 1,000 TCID $_{50}$/0.5 ml; 8 HID_{50} estimated.

Table 19.—*Vaccine Groups and Route of Inoculation of Vaccine*

Vaccine group	Route of inoculation [1]	
	Subcutaneous	Naso-pharyngeal
Jetgun	A_2/HK	B/Mass/3/66.
Spray	B/Mass/3/66	A_2/HK.
Combined (jetgun and spray).	A_2/HK	A_2/HK.
Control	B/Mass/3/66	B/Mass/3/66.

[1] 400 CCA units of each vaccine administered by route shown.

Table 20.—*Influenza Illness Rates in Vaccinated Psychiatric Patients Exposed to Infection During Naturally Occurring A_2/HK Influenza Epidemic*

Vaccine group	Number of persons	Reported	Number of patients		Influenza attack rate/100
			Tested	Positive	
Control	87	14	14	11 [a]	14.7
Spray	89	12	12	10 [a]	12.2
Jetgun	90	5	4	4	5.5
Combine (jetgun and spray)	88	6	5	4	5.4

Results. When frequency of illness in the vaccinated groups was compared to that in the control group saline, a significant reduction was noted in the group receiving the X–31 vaccine ($p=0.02$) and a borderline reduction in the group receiving the Aichi strain vaccine ($p=0.06$). This is summarized in Table 21.

Table 21.—*Occurrence of Illness in Vaccinated Volunteers Challenged With Live A_2/Aichi Strain Vaccine*

Vaccine group	Number of volunteers	Virus isolated	Results of challenge inoculation		
			4-fold antibody rise	Number ill	Number febrile
Saline Control	14	11	11	6	4
A_2/Aichi	15	5	4	1	1
A_2/X–31	14	2	0	0	

b. *Safety.*

(1) *Animals.* See generic review. COFAL test are described.

(2) *Humans.* The submission contains an excellent summary of studies performed by Eli Lilly and Co. staff in 1967 which indicates that Zonomune produce fewer local and systemic adverse reactions than the previous product. Comparisons of Zonomune with other purified vaccines have been submitted by other drug companies which confirm these results.

Data on serious adverse reactions are not submitted. There is at least one report (not mentioned in the submission) of meningoencephalitis following Zonomune (Ref. 6).

c. *Benefit/risk.* See generic review.

d. *Labeling.* See generic review.

3. *Conclusions—recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Influenza Virus Vaccine, Bivalent (Fluax) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* The package circular states FLUAX—(Influenza Virus Vaccine, MSD). Bivalent Types A & B, Filter and Zonal Centrifuge Purified, is an aqueous suspension containing the recommended contemporary strains of influenza viruses. The vaccine virus is grown in embroynated chicken eggs and purified by a series of physical separation steps. Cellular residues and other extraneous particulate contaminants are removed by means of sedimentation-clarification of the extra-embryonic fluid. The resultant fluid is further freed of undesirable (non-viral) materials by selective filtration through controlled pore size filters. The final purification step consists of isopycnic banding of the virus in sucrose in a flow zonal centrifuge with selective recovery of influenza virus. Sedimentation analysis of the zonally fractionated vaccine demonstrates the absence of impurities. Formalin is the inactivating agent. Thimerosal 1:10,000 is added as preservative.

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.*

a. *Efficacy.*

(1) *Animals.* Potency data are provided, with specific reference to stability of vaccines.

(2) *Humans.* Only one study of antigenicity and reactogenicity was presented by the manufacturer for the product as presently prepared.

Study 234 (1969) involved two lots of

zonal centrifuge-filter purified aqueous vaccine containing A_s/Aichi/2/68, 400 CCA/ml and B/Mass/3/66 and 300 CCA/ml.

Two 0.5 ml doses were given subcutaneously at a 1-month interval to males 17 to 69 years of age. The serologic responses observed are summarized in Table 22.

Table 22.—*Serologic Responses to Vaccine*

	Number with 4-fold greater response/total number tested (by month)													
	Initially seronegative				All vaccinees				GM titer of HI antibody by month					
	A_s/Aichi		B/Mass		A_s/Aichi		B/Mass		A_s/Aichi			B/Mass		
	Months													
	1	2	1	2	1	2	1	2	0	1	2	0	1	2
Lot number of vaccine:														
1121	13/21	13/20	5/5	4/5	14/33	19/31	8/33	5/31	3	16	20	16	42	31
4/98450	(62%)	(65%)	(100%)	(80%)	(42%)	(61%)	(24%)	(19%)						
1121	16/22	16/23	2/3	1/3	17/33	18/34	5/33	3/34	3	22	22	19	37	30
598451	(73%)	(70%)	(67%)	(33%)	(52%)	(53%)	(15%)	(9%)						

In addition to this study, the following statement is made in a Merck Sharp & Dohme supplemental submission:

There are no data to indicate the protective capacity of the specific product in response to natural infection or artificial challenge. However, it is fairly well accepted among influenza virus experts that a level of circulating hemagglutination-inhibition antibody of 1:40 or greater generally correlates with protection. In a series of 6 clinical studies which incorporated zonal centrifuge-purified aqueous type influenza virus vaccine as control, and which involved about 450 persons, approximately 80 percent of the subjects had a 1:40 or greater titer of HI antibody to the A_s influenza virus strain and about 50 percent had similar activity to the B strain. It would be expected that the same general level of protective antibodies would be generated in the population at large.

The data from these six clinical studies mentioned are not available. However, there is recent information obtained by the Bureau of Biologics that influenza vaccine produced by this manufacturer is similar in antigenicity to other whole virus influenza vaccines.

In spite of the claim in the submission that "there are no data to indicate the protective capacity of the specific product," there is one published report where a Merck Sharp & Dohme vaccine was used in April 1969 to prevent Hong Kong influenza (Ref. 7). This vaccine, which was not prepared by the current process (Zonal centrifugation), contained the A_2/Aichi/2/68 strain (CCA unitage unknown) and was administered subcutaneously in 1.0 ml doses.

Some 1,254 Bantu subjects received the vaccine and 413 received placebo; all worked in the same factory. An outbreak of influenza-like disease was observed in May 1969, some cases of which were proved to be Hong Kong influenza. The incidence of clinical influenza in the control group was 31/1,000 and in the vaccinated group was 5/1,000.

b. *Safety.* (1) *Animals.* The released vaccines meet Federal requirements.

(2) *Humans.* In the study summarized in Table 22 above, there were only two cases of local erythema and essentially no febrile or other adverse reactions greater than those noted in controls. It is disturbing, however, that local swelling or induration, and malaise, headache, chills, etc. were apparently not looked for in this study. Additional information on human safety is, however, provided in recent studies performed by the Bureau of Biologics and the manufacturer. In these trials the rates of reactogenicity of this vaccine were similar to those of other whole virus vaccines.

c. *Benefit/risk.* See generic review.

d. *Labeling.* See generic review. One suggested change is that the reduction in volume (from 1.0 to 0.5 ml) should not be claimed to be an unusual feature of the vaccine, since this has been achieved by all companies presently marketing influenza vaccines.

3. *Conclusions.* a. *Critique.* This Merck Sharp & Dohme submission suffers from the defects seen in others from the same manufacturer. No protective data were submitted by the manufacturer. The matter of protection is dismissed with the statement, "Influenza virus vaccines have been studied so thoroughly through the years that essentially all published efficacy data have a direct or indirect influence on all available commercial vaccines.".

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Influenza Virus Vaccine, Bivalent (Fluzone) Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* The package circular states:

Influenza Virus Vaccine (Zonal Purified) is prepared from the allantoic fluid of chick embryos infected with Types A_2 and B influenza viruses. Each virus is inactivated with formaldehyde, and concentrated and purified in a linear sucrose density-gradient solution using a continuous flow ultracentrifuge. The virus is then further purified by chemical means. The resulting vaccine is more highly purified than vaccine processed by the usual differential centrifugation method as determined by total nitrogen content and electron microscopic studies * * *. Thimerosal 1:10,000 is added as a preservative. The final product contains less than two percent sucrose.

A. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.* a. *Efficacy.* (1) *Animals.* No potency data submitted. See generic review.

(2) Humans. Most of the references cited regarding zonal purified vaccines report studies which used vaccines produced by other companies. Two of the citations in the submission refer to data regarding the antigenicity of the A component present in formulations produced by Merrell-National, and a third citation is to a paper on the protective capacity of the A component. No data of any kind were submitted for the B component.

(i) *Antigenicity.* Monovalent vaccines were administered to recruits at the Great Lakes Naval Training Station by Dr. Nicola Tauraso, and the antibody reponse measured 30 days later. The results are summarized in Table 23.

Table 23.—*Antibody Reponse to Two Lots of Zonally Centrifuged A_2/Aichi/2/68 Vaccine, 0.5 ml per Subcutaneous Dose*

Vaccine lot No.	CCA dose [1]	Initially geometric mean titer		Seronegative converting		Initially geometric mean titer		Seropositive converting	
		Pre	Post	Number	Percent	Pre	Post	Number	Percent 4-fold
7145 Z	787	1.0	64	10/10	100	64	256		2/5
7151 Z	772	1.0	208	8/8	100	23	418	7/7	
	100								

[1] These data are from the producer's submission (Table D of attachment 4) An addendum to the attachment stated: "Lots #7145 and 7151 were prepared by zonal purification and contained 400 CCA units per dose (0.5 ml)."

In a second study bivalent vaccine containing 700 CCA units of A/Aichi/2/68 (H_3N_2) and 300 CCA units B/Mass/1/71 per 0.5 ml dose was given subcutaneously to 100 males 24 to 93 years of age, 91 of whom had serologic specimens tested (median age 51) (Ref. 8). Serum antibody responses after 3 weeks were as follows: 62 percent of men with initial serum HI titers of ≤ 160 showed a four-fold or greater antibody response, and the GMT of the entire group rose from 65 prior to vaccination to ≥ 212 following vaccination. Hemagglutination inhibition responses occurred in all seven men with undetectable preexisting antibody (< 10). This group had a final GMT of 83. Antibody rises were seen in 24 of 27 (89 percent) men with prevaccination titers of ≤ 20. Of 48 volunteers with initial HI titers less than a "protective" level (80), 36 (75 percent) reached ≥ 80 in the serum after vaccination.

Nasal antibody was measured in 18 men. One-half showed a four-fold or greater antibody rise.

(ii) *Efficacy.* Stiver et al. administered bivalent vaccine containing 600 CCA units of A_2/Aichi/2/68 antigen and 400 CCA units of B/Mass/3/66 antigen to Air Force recruits during the first 6 months of 1972 (Ref. 9). An outbreak of A_2/Denver/1/72($=A_2$/England/72) infection occurred several months after the vaccine was administered. The overall attack rate of influenza was 46.0 per 1,000 in 2,955 unvaccinated men, and 18.4 per 1,000 in 979 vaccinees, a reduction of 60 percent.

b. *Safety.* (1) *Animals.* No data submitted; the product meets FDA requirements. See generic review.

(2) *Humans.* Data available for the two antigenicity trials cited above indicate acceptable percentage of mild to moderate local and systemic reactions. Only six medical complaints were reported for 2 distribution years during which 5 million doses were distributed. COFAL testing is described.

c. *Benefit/risk.* See generic review.

d. *Labeling.* See generic review.

3. *Conclusions.* a. *Critique.* The study by Stiver et al. provided efficacy data which show a 60 percent reduction in illness even when the epidemic strain was not homologous to the vaccine strain (Ref. 9). There is recent information obtained by the Bureau of Biologics that influenza vaccine produced by this manufacturer is similar in antigenicity to other whole virus influenza vaccines.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Influenza Virus Vaccine, Bivalent (Fluogen) Manufactured by Parke, Davis & Co.

1. *Description.* The package circular states:

> FLUOGEN (Influenza Virus Vaccine, Bivalent, Ether-Extracted Antigen) (Types A and B) is composed of the antigen of the strains of influenza viruses recommended* * *. In addition to initial virus purification steps by filtration, ultracentrifugation, and zonal centrifugation, treatment of the influenza virus vaccine concentrate with ethyl ether disrupts the virus, removes a high proportion of egg protein, ribonucleic acid, lipids, and other pyrogenic substances. From this process, the active immunizing antigens are retained at full potency.

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.* a. *Efficacy.* (1) *Animals.* Potency data were not provided by the manufacturer. Data obtained by the staff of the Bureau of Biologics showed clearly that the Parke-Davis & Co. vaccine, in equivalent CCA content, produced lower mean antibody levels in mice than did whole virus vaccines (refs. 10 and 15). It was estimated that 10 to 100 times the quantity of antigen in terms of CCA units, was required to produce the same effect with ether-split as with whole virus vaccine.

(2) *Humans.* Limited data were provided in the original submission concerning the antigenicity of the product as currently prepared (including the zonal purification step). One supplementary submission included an analysis of a study in children 5 to 14 years of age who, in December 1972, received one or two inoculations (0.5 milliliters each) of bivalent vaccine containing either the X–31 recombinant of A2/Aichi (700 CCA) or the X–37 recombinant of A2/England (700 CCA) plus B/Mass (300 CCA). Diphtheria-tetanus controls were included. The 1-week geometric mean (GM) antibody titers of this group of children are listed in Table 24.

Table 24.—*Antigenicity in Children of X–31 Recombinant of A_2/Aichi and the X–37 Recombinant of A_2/England Viruses*

Vaccine group	Number of children	Serum spec	GMT of HI antibody to virus strain				
			X–31	Aichi	X–37	England	B/Mass
X–31	219	Pre-vacc.	55	57	41	26	16
and B		1 wk	213 (3.89)	218 (3.86)	158 (3.86)	114 (4.34)	53 (3.27)
X–37	228	Pre-vacc.	51	54	37	25	18
and B		1 wk	276 (5.37)	307 (5.65)	293 (7.85)	219 (8.92)	66 (3.61)
Diph.–	213	Pre-vacc.	57	57	40	25	18
		1 wk	53 (0.94)	57 (1.00)	38 (0.98)	28 (1.10)	18 (1.00)

[1] Figures in parentheses show the fold-rise in antibody titer.

The FDA material contains data on a comparative trial of the antigenicity of a nonzonal ether-extracted vaccine with the present vaccine (protocol 150 to 152). The two types of vaccine, either with our without aluminum phosphate adjuvant, were found to be of equivalent antigenicity. Table 25 illustrates the findings on the antigenicity of a nonadjuvanted, zonal centrifugation product, an A2/Aichi/X–31 vaccine.

Table 25.—*Antibody Response to a Nonadjuvanted, Zonally Centrifuged A_2/Aichi/X–31 Vaccine*

Number of volunteers[2]	Route of inoc. (0.5 ml)	HI antibody response[1] to:					
		A_2/Aichi/X–31 (400 CCA units)			B/Mass (300 CCA units)		
		Pre-vacc.	Post-vacc.	Fold-rise	Pre-vacc.	Post-vacc.	Fold-rise
11	Subcutaneous	32.05	178.75	5.58	7.85	21.45	2.73
27	Intramuscular	44.40	304.85	6.87	7.55	46.60	6.17

[1] Expressed as geometric mean titer.
[2] Prisoners, aged 21–65 years.

The superiority of the intramuscular route shown in Table 25 above is reflected in all vaccines (nonzonal and aluminum phosphate absorbed) used in this study and is significant when all the data are pooled ($p<0.05$). Considerable data are available concerning the antigenicity of earlier ether-split vaccines, but the details are not included here. In one trial comparing Fluogen with Merck Sharp & Dohme and National Drug zonal purified vaccines, the fold-rise with Fluogen (A_2/Aichi) was 7.84 vs 3.36 and 3.97, respectively, and the fold-rise with Fluogen (B/Mass) was 4.63 vs 3.51 and 2.41. The CAA content in the bivalent Fluogen was greater than that of the two whole virus vaccines (849 vs 743 and 481 for Merck Sharp & Dohme and National products, respectively). This fact might have had some influence on the comparative antibody respo: ses, but it would certainly not have entirely accounted for the differences observed.

Because of the inferior antigenicity of nonadjuvanted ether-tween and other subunit vaccines in mice, there is considerable interest in the response to such vaccines of human subjects without previous influenza experience. As noted in the generic statement, seronegative individuals may or may not have had previous influenza infection. Few adults, or even school aged children, have escaped previous infection with both A and B strains of influenza, and most are, therefore, primed for an anamnestic response to any influenze vaccine they may receive. Several studies of such seronegative subjects have been provided both by the Bureau of Biologics and in supplementary submissions by the manufacturer. The results of these are summarized in Tables 26D through 26G.

A comparative trial of licensed influenza vaccines was performed by the Bureau of Biologics at the Arkansas Children's Colony (Ref. 12). The subjects were mentally retarded children and adults, 6 to 33 years of age and normal adults, ages 18 to 88. The vaccines were the bivalent A/England/72-B/Mass/71 (700 and 300 CCA units/0.5 ml claimed, 1240/0.5 ml total measured) and B/Hong Kong (500 CCA units/0.5 ml claimed, 576/0.5 ml measured). Dosage was 0.5 ml for those over 12 years and 0.25 ml for those 6 to 12 years. Bivalent vaccine was administered subcutaneously on day zero and the B/HK vaccine at 6 weeks. It should be noted that it is recommended on the package circular that Parke-Davis' product be administered intramuscularly, and that the superiority of the intramuscular route had been previously demonstrated from Fluogen (R) (see above).

In those individuals with measurable pre-existing HI antibody (>1:8), there was no difference between the response to ether-tween split vaccine and the whole virus products. In those with prevaccination levels <1:8, the Parke-Davis products stimulated antibody levels which were, in most cases, lower than those induced by whole virus vaccines (the results are shown in Table 26 below).

Table 26.—*Antibody Response to Whole Virus Vaccine and the Ether-Tween Split Vaccine in Individuals With Prevaccination HI Antibody Titers of <1:8*

Vaccine	Seroconversion rates and HI antibody response at postvaccination intervals and vaccine components shown					
	A[2] England		B/Mass		B/Hong Kong	
	6 wks	12 wks	6 wks	12 wks	6 wks	12 wks
Seroconversion						
Whole Virus	86/100	87/100	66/84	77/84	80/100	130/169
P–D ether-split	19/23	[1]16/23	12/16	11/16	[1]12/48	33/45
Geometric mean antibody titers (reciprocal)						
Whole virus	22.8	20.4	17.4	22.3	8.5	13.4
p–D ether-split	17.5	13.3	16.6	[2]13.9	6.0	16.2

[1] $0.05<p<0.1$.
[2] $p<0.01$

More recently a double-blind controlled trial of influenza vaccines containing monovalent A/Swine strains ws carried out in multiple centers throughout the country. Subjects were divided into the following age groups for pusposes of analyses: those over 23 years of age (and thus born before 1953 and likely to have experienced prior infection with influenza viruses preceding the Asian strains); those 17 to 23 years old; and children 6 to 10 years old. Vaccines were adjusted so that potency, as measured by the CCA test, was comparable in the four preparations tested. Two whole virus preparations (Merrell-National and Merck Sharp & Dohme) and two submits vaccines (Wyeth and Parke-Davis) were tested. Vaccine was administered in most individuals by intramuscular injection and in some by jet injection. The results, shown in Tables 26A, 26B, and 26C,

demonstrate clearly that a single inoculation of subunit vaccines in the dosages tested was highly antigenic in the oldest group, inferior to whole virus preparations in young adults, and almost totally ineffective in children. Subsequently, it was demonstrated that a booster dose of subunit vaccine administered 4 or more weeks after the first does stimulated antibody production approximately equivalent to that induced by two doses of whole virus vaccine, even in children as young as 3 years of age.

Table 26A.—*Response to A/NJ Vaccine in Children Ages 6 to 10*

Manufacturer	Dose	No. subjects	Percent with HI antibody titers ≥10	≥20	≥40
Wyeth	100	[illegible]	31	[illegible]	0
	200	43	33	11	3
	400	44	[illegible]	23	5
Parke-Davis	100	44	7	5	2
	200	42	14	12	9
	400	43	14	5	2
Merrell-National	100	[illegible]	82	69	44
	200	42	85	74	50
	400	34	85	82	59
Merck Sharp & Dohme	100	35	91	86	77
	200	[illegible]	100	100	50
	400	0			
Placebo		40	5	3	0

Table 26B.—*Post Vaccination Antibody Status of All Participants 23 Years and Under*

Manufacturer	Dose	No. subjects	Percent with HI antibody titers ≥10	≥20	≥40
Wyeth	200	43	44	35	28
	400	42	74	64	41
	800	40	[illegible]	50	33
Parke-Davis	200	41	46	44	37
	400	41	54	32	22
	800	[illegible]	71	50	45
Merrell-National	200	46	80	54	46
	400	32	91	75	56
	800	42	91	67	48
Merck Sharp & Dohme	200	[illegible]	92	74	58
	400	49	100	96	86
	800	29	100	93	90

Table 26C.—*Postvaccination Antibody Status of All Participants 24 Years and Older*

Manufacturer	Dose	No. subjects	Percent with HI antibody titers ≥10	≥20	≥40
Wyeth	200	111	93	85	74
	400	106	94	90	85
	800	98	97	94	91
Parke-Davis	200	109	97	96	92
	400	100	96	93	90
	800	116	95	95	93
Merrell-National	200	96	[illegible]	84	71
	400	115	97	89	83
	800	[illegible]	97	95	87
Merck Sharp & Dohme	200	119	[illegible]	98	90
	400	106	99	[illegible]	92
	800	108	99	97	93

Comparative studies in seronegative children and adults immunized with H_3N_2 antigens have demonstrated the equivalence of this product, as presently manufactured, to whole virus vaccines. The results of one such trial performed by the manufacturer are shown in Tables 26D and 26E (from Parke-Davis Protocol 150–66). The subjects were healthy hospital employees. Another trial, this one in children is summarized in Tables 26F and 26G. The children were 4 to 13 years of age, and the average age of those receiving Fluogen (R) or whole virus vaccines was 8.25 or 8.09, respectively (Parke-Davis Protocol 150–73). In addition, several other trials have been performed in children, young adults, and, in one instance, elderly subjects.

Table 26D.—*Distribution of 3-Week Postvaccination HI Titers Versus A/Port Chalmers Virus of Seronegative Subjects Given Fluogen or Whole Virus Vaccines: 1974–75 Formulae*

Vaccine	Postvaccination A/P.C. HI titer <10	10–20	40–80	160–320	>640	Geometric [illegible]	Percent with ≥4X increase
Parke-Davis (16) [1]	1	1	3	[illegible]	2	129	94
Merck Sharp and Dohme (20)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	113	[illegible]
Merrell-National (17)	[illegible]	0	7	7	3	[illegible]	100
Lilly (21)	0	3	7	[illegible]	[illegible]	131	[illegible]

[1] Number of seronegative subjects.

Source: Final Report, P–D Protocol 150–66. Subjects were adults all of whom received 0.5 ml of intramuscular vaccine containing approximately 700 CCA units of A/PC/1/73 and 500 CCA units of B/HK/5/72 per 0.5 ml. Measured potency not reported.

Table 26E.—*Distribution of 3-Week Postvaccination HI Titers Versus B/Hong Kong Virus of Seronegative Subjects Given Fluogen or Whole Virus Vaccines: 1974–75 Formula*

Vaccine	Postvaccination, B/HK HI titer <10	10–20	40–80	160–320	≥640	Geometric mean	Percent with ≥4X increase
Parke-Davis (25) [1]	1	5	8	8	3	92	88
Merck Sharp and Dohme (30)	0	1	15	10	4	139	100
Merrell-National (29)	3	3	14	8	1	57	90
Lilly (25)	2	3	9	7	4	82	88

[1] Number of seronegative subjects.

Source: Final Report, P–D Protocol 150–66. See source note, Table 26D.

Table 26F.—*Distribution of 4-Week Postvaccination HI Titers Versus A/Scotland Virus of Seronegative Children Given Fluogen or Whole Virus Vaccines: 1975–76 Formula*

Vaccine	Postvaccination A/Scot HI titer <10	10–20	40–80	≥160–320	640	Geometric mean	Percent with ≥4X increase
Fluogen (21) [1]	2	4	2	9	4	104	86
Whole virus [2] (32)	0	3	5	20	4	171	94

[1] Number of seronegative subjects.
[2] Merck Sharp & Dohme and Merrell-National.

Source: Final Report, P–D Protocol 150–73. Children were 4–13 years of age and received 0.5 ml (>10 years old) or 0.25 ml (<10 years old) of intramuscular vaccine containing approximately 350 CCA units A/PC/1/73, 350 CCA units A/Scotland/840/74, and 500 CCA units B/HK/5/72 per 0.5 ml. Measured potency of the vaccine was not reported. Bleeding before and 4 weeks after immunization.

Table 26G.—*Distribution of 4-Week Postvaccination HI Titers Versus B/Hong Kong Virus of Seronegative Children Given Fluogen or Whole Virus Vaccines: 1975–76 Formula*

Vaccine	Postvaccination B/HK HI titer <10	10–20	40–80	160–320	≥640	Geometric mean	Percent with ≥4X increase
Fluogen (54) [1]	1	9	20	21	3	80	94
Whole virus [2] (71)	1	8	28	29	5	105	96

[1] Number of seronegative subjects.
[2] Merck Sharp & Dohme and Merrell-National.

Source: Final Report, Parke-Davis. Protocol 150–73. See source note, Table 26F

There are efficacy data for the present product derived from the school study described above. In this study, influenza vaccines or diphtheria tetanus toxoid

vaccined as a placebo were administered on December 4, 1972, and a booster to those available on January 8, 1973. A small outbreak of A2/England influenza occurred in the school during early January, detected by influenza virus recovery in 10 of 23 cases and rises in HI antibody during this period in 19 percent of the placebo control children. The outbreak, and the efficacy of the vaccine, were measured primarily by school absenteeism. Comparison was made between (1) children who received either of the two influenza vaccines, and (2) those who received a diphtheria-tetanus vaccine plus (3) a larger "control" group of children who attended another school in the same community and received no vaccine. The following is from the discussion section of the manufacturer's submission:

Average total days of absence/100 children/ 15 day observation interval (1500 child-school days) are collected below [presented here in Table 26H], for the influenza vaccinee and nonvaccinee groups respectively, as a function of observation interval. Using these values, various estimates of vaccine efficacy can be derived.

Table 26H.—*Protective Efficacy of Vaccine Evaluated on Basis of School Absenteeism*

Vaccine group (observation interval)	Total number children	Days of absence/1,500 child-days of school		
		1 and 2 [1]	3 [2]	4 and 5 [3]
X-31 plus X-37 vacinees.	458	68.7	127.3	92.1
Placebo plus controls.....	612	61.4	192.9	91.1

[1] Nov. 8, 1972 to Dec 19, 1972.
[2] Jan. 3, 1973 to Jan 23, 1973.
[3] Jan. 24, 1973 to Apr. 7, 1973.

1. From the interval 3 data alone, one obtains (192.9–127.3)/192.9 = 34.0%, as the protection ratio without correction for noninfluenza associated background absenteeism.

2. Subtraction of the average, pre-Christmas absentee rates from the interval 3 data gives a protection ratio of (131.5–58.6)/131.5 = 55.4%, corrected for pre-Christmas absentee levels.

3. However, since background absentee rates differed significantly between the first two and last two intervals [see Table 26H], and since the latter period was closest to and continuous with the third, or epidemic interval, post-Christmas absenteeism (intervals 4 and 5) seems the most realistic backgound against which to judge the superimposed, influenza-associated, effect. Correction of the interval 3 data for the post-Christmas background yields (101.8–35.2)/101.8 = 65.4% as the most reasonable estimate of vaccine efficacy (against absenteeism) in this student population.

Thus, depending on the choice of background, efficacy estimates from a low of 34.0% (without correction from backgound absenteeism), to a high of 65.4% (correcting from immediately adjacent backgound absenteeism) are possible; with the latter seeming to provide the most reasonable value.

This study appears to show a protective effect of Fluogen(R) on epidemic influenza in school children. However, because school absenteeism, rather than true infection and illness rates, was used as an index of vaccine efficacy, and because the control group was diluted with a large number of children from a different school who were not true controls, the Panel considers that further efficacy trials are necessary to corroborate this finding.

Other protection data available refer to older either-split vaccines but the studies were not very well controlled (Refs. 16 and 17).

b. *Safety.*

(1) *Animals.* The vacine is said to be free of live virus and to have passed the general safety tests.

(2) *Humans.* At a time when vaccines were made from Sharples concentrated virus and when local and systemic reactogenicity posed a serious barrier to their general acceptance, ether-Tween treatement clearly reduced the number of febrile response, particularly in children (Ref. 18). More recently, further data have been submitted (Parke-Davis Protocols 150–66 and 150–73) to support the contention that febrile responses, and probably other systemic reactions as well, are less frequent following Fluogen (R) than after present zonally purified vaccines. This difference appears to be particularly clear in children. The results of Protocol 150–66, where Fluogen (R) was compared with three commercial zonally purified whole virus vaccine in healthy hospital employees are shown in Table 26I. Similar results in school children (Protocal 150–73) are shown in Table 26J.

Table 26I.—*Distribution of Subjects With a Local or Systemic Reaction 24 Hours After Vaccination*

	Number of subjects with local reaction			Number of subjects with systemic reaction		
	Yes	No	Total	Yes	No	Total
Fluogen	60	26	86	19	67	86
Whole virus	207	50	257	88	169	257
Total	267	76	343	107	236	343
Chi squared	3.7			3.9		
p	=.053			>.05		
	(1)			(2)		

[1] Not significant.
[2] Significant.
Source: See source note to Table 26D.

Table 26J.—*Distribution of Children With a Local or Systemic Reaction 24 Hours After Vaccination*

	Number of children with local reaction			Number of children with systemic reaction		
	Yes	No	Total	Yes	No	Total
Fluogen	37 [1](31)	83	120	14 (12)	106	120
Whole virus	55 (43)	73	128	36 (28)	92	128
Total	92	156	248	50	198	248
Chi squared	3.4			9.4		
p	=.065			>.01		
	(2)			(3)		

[1] Numbers in parentheses are percent showing reaction.
[2] Not significant.
[3] Significant.
Source: See source note to Table 26F.

The producer has received 45 written complaints concerning reactions for over 22.8 million doses distributed (of earlier formulations).

c. *Benefit/risk.* See generic review.

d. *Labeling.* See generic review.

3. *Conclusions.* a. *Critique.* This vaccine is antigenic in individuals who have had prior experience with related influenza strains. This statement appears to hold true whether or not there is measurable preimmunization homologous HI antibody. In those without such experience, the use of this vaccine requires several doses to stimulate protective levels of HI antibody.

One study of protective efficacy has been reported for the vaccine as presently manufactured. A significant protective effect, measured in school absenteeism, was shown in children who, as a group, had responded with the development of antibody. The findings require corroboration in further efficacy trials. The Panel recognizes the difficulty of proving efficacy for influenza vaccines, particularly in interepidemic years, but such proof is clearly needed.

Evidence supports the opinion that this vaccine is less reactogenic than whole virus products.

b. *Recommendation.* (1) The total body of evidence, including that recently developed in tha national dose-response trial of A/swine vaccines, indicates that split virus vaccines are adequately antigenic in persons with appropriate prior immunologic experience. In the case of H_3N_2 and, presumably B/HK antigens, these include most school-age children and older persons. In the case of the A/swine antigen, adequate response in persons under 24 years of age requires more than one dose.

The Panel recommends that this product be placed in Category I and that the license be continued, subject to labeling which clearly indicates the necessity for more than one dose in immunologically inexperienced persons.

(2) Further efficacy trials should be designed and implemented by the manufacturer.

Influenza Virus Vaccine, Bivalent (Chromatograph and Filter Purified Subvirion Antigen) Manufactured by Wyeth Laboratories, Inc.

1. *Description.* The package circular states:

Influenza Virus Vaccine, Bivalent, (Chromatograph and Filter Purified Subvirion Antigen) Wyeth, contains the immunizing antigens of the contemporary influenza virus strains recommended by the U.S.P.H.S. . . . The vaccine virus is grown in the extraembryonic fluids of embryonated chicken eggs and then processed to final vaccine by an improved method different from the usual differential centrifugation techniques yielding whole-virion vaccines. The harvested virus is concentrated and refined by a column chromatographic procedure, retaining full antigenicity while losing large amounts of contaminating egg proteins, lipids, nucleic acids and other amorphous and cellular residues arising in the egg fluids. At the same time, addition of tri(n)butyl phosphate and Polysorbate 80 U.S.P. to the column-eluting fluids effects disruption of the virus to smaller, fully antigenic sub-unit particles. The recovered sub-virion suspension is freed of substantial portions of the disrupting agents by dialysis, and of other undesirable materials by selective filtration through membranes of controlled pore size. In the course of preparation, formaldehyde solution (no more than 1:10,000 in the final product) is used, and thimerosal, 0.01 %, is added as a preservative.

a. *Recommended use.* See generic review.

b. *Contraindications.* See generic review.

2. *Analysis.* a. *Efficacy.*

(1) *Animals.* Data obtained by the staff of the Bureau of Biologics and published in an article by D. W. Barry et al. (Ref. 10) showed clearly that the Wyeth Laboratories vaccine, in equivalent CCA content, produced lower mean antibody levels in mice than whole virus vaccines. Data subsequently submitted by Wyeth Laboratories, with the caveat that the mouse can not be equated with man, showed that the antibody response in mice (both neutralizing and HI) was slower with subvirion vaccine than with whole virus vaccine, but that antibody levels at 4 to 8 weeks, although still lower, were more nearly comparable.

(2) *Humans.* Tables 26A, 26B, and 26C (see review of Parke-Davis influenza virus vaccine) present antigenicity data from recent A/swine vaccine clinical trials. Tables 27 through 34 summarize data from earlier antigenicity studies with A and B antigens. Tables 35 and 36 summarize two studies of protection, one in young adults and one in the elderly. In addition, two studies have noted that this product stimulated neuraminidase-inhibiting antibody, and that among persons lacking prevaccination serum antibody to the hemagglutinin antigen in whole virus or subvirion vaccines, the numbers of responders to the neuraminidase antigen were comparable in each vaccine group (approximately 50 percent) (Refs. 19 and 20).

Table 27.—*Antigenicity Study by Wyeth of a TNBP Purified Bivalent Vaccine* [1]

Vaccine lot No.	Route of innoculation (0.5 ml)	Serum pairs	Virus type	Results initial GMT	Responses		
					Number	Percentage	Fold-rise
78BIV	Subcutaneous	12	A	50	11	92	7.1
00701			B	40	11	92	10.0
78BIV	Intramuscular	10	A	41	8	80	13.2
00702			B	71	10	100	15.1

[1] Study units were 400 CCA units A_2/Aichi/2/68 and 300 CCA units B/Mass/3/66 in 0.5 ml. Subjects were male and female students, 18 to 26 years of age.

Table 28.—*Results of 3 Combined Antigenicity Studies, 1 Including Controls, by Wyeth Laboratories* [1]

Vaccine lot number	Serum pairs	Antibody responses to					
		A_2/Aichi/2/68			B/Mass/3/66		
		No. and percent > 4-fold rise	GMT		No. and percent > 4-fold rise	GMT	
			Initial titer	Rise in titer		Initial titer	Rise in titer
78BIV-005	73	71 (97)	57	35.5	67 (92)	104	21.8
78BIV-006	73	67 (92)	37	34.8	67 (92)	76	27.4
78BIV-007	85	78 (91)	53	18.1	83 (95)	96	25.6
Placebo	69	3 (4.3)	36	1.5	16 (23)	80	2.5

[1] Vaccines, dosage, and strains were as in Table 27. The population was male and female students and recruits, 17–26 years of age.

NOTE.—Figures in parenthesis are present.

Table 29.—*Antigenicity Studies by Phillips et al. (Ref. 21) of a Bivalent Vaccine in Children* [1]

	Virus type	Antibody response		
		No. and percent ≥4-fold rises	GMT	
			Pre-vaccination	4 weeks post-vaccination
Number of children:				
33	A	31 (94)	6.6	112.2
33	B	21 (64)	1.2	19.9

[1] The Vaccine used was as in table 27, given in varying doses from 350 to 1400 CCA units. Subjects were Children 5–9 years of age.

NOTE.—Figures in parenthesis are percent.

Table 30.—*Antibody Response Elicited by Varying Doses of a Bivalent Vaccine in Adults From Studies by Ruben et al. (Refs. 22 and 23)* [1]

Number of CCA units given, virus type A/B	Route	Antibody response			
		Number with ≥4-fold rises to virus type		Initial/final HI antibody titer	
				Virus type	
		A	B	A	B
40/30	Intradermal	9/9	7/9	16/167	25/239
400/300	Subcutaneous	11/14	13/14	36/247	89/1,178
400/300	Intramuscular	9/10	9/10	25/513	200/1,590
800/600	do	10/10	8/10	20/289	250/1,820
1,600/1,200	do	10/10	4/5	16/390	150/2,400
3,200/2,400	do	10/11	8/11	8/[illegible]	25/303
6,400/4,800	do	9/9	8/9	4/258	25/[illegible]

[1] The vaccine used was the same as in Table 27. The population was male and female students and recruits, 18 to 25 years of age.

Table 31.—*Comparative Antigenicity Studies in Children and Adults of a Whole Virus and Split Virus Vaccine From a Study by Barry et al. (Ref. 10)* [1]

Vaccine administered	Response of seronegative individual to					
	A/England		B/Mass		B/Hong Kong	
	6 weeks	12 weeks	6 weeks	12 weeks	6 weeks	12 weeks
Seroconversion						
Whole virus	86/100	87/100	66/84	77/84	69/169	130/169
Wyeth split	[2] 15/23	[2] 14/23	14/21	16/21	19/52	40/52
Geometric mean titers (reciprocals)						
Whole virus	22.8	20.4	17.4	22.3	6.5	13.0
Wyeth split	17.0	[3] 12.6	14.0	[3] 13.5	6.6	13.0

[1] The vaccine used were A/England—B/Mass bivalent (700 and 300 CCA units claimed per 0.5 ml, 1,120 total measured at zero time) and B/Hong Kong (500 CCA units claimed per 0.5 ml, 785 measured at 6 weeks). The population was mentally retarded subjects 6 to 33 years old and normal adults 18 to 88 years old.

[2] $p=0.05$ in comparison to whole virus vaccines.

[3] $p=0.01$ in comparison to whole virus vaccines.

Table 32.—*Antigenicity of Bivalent Subunit Vaccines in Naval Recruits with Varying Levels of Pre-existing Antibody From a Study by Rosenbaum, Data Submitted by Wyeth* [1]

Initial titer	HI Ab increases			
	None	≥2-fold	≥4-fold	GM increase (fold)
A$_2$/Aichi				
<lowest dilution (<1:10)	0/30	30/30 [2](100)	28/30 [2](93)	40.4x
Placebo group (<1:10)	5/9	4/9	2/9	1.7x
=lowest dilution (1:10)	0/24	24/24 [2](100)	24/24 [2](100)	26.2x
Placebo group	0/11	0/11	0/11	1.0x
≥lowest dilution (≥1:97.8)	3/94	91/94 [2](97)	87/94 [2](93)	27.5x
Placebo group (<1:95.8)	25/40	15/40	1/40	1.3x
B/Mass				
≥lowest dilution (1:127.7)	3/144	141/144 [2](98)	130/144 [2](91)	30.6x
Placebo group (1:98.6)	32/67	35/67	22/67	3.5x

[1] The vaccine, dosage, and strains used were as in Table 27.
[2] Percent.

Table 33.—*Antigenicity of Whole Virus and Subunit Vaccines in Adults* [1]

	Subunit						Whole virus				
	Conversion		Titer		Fold-rise	Number	Conversion		Titer		Fold-rise
	≥2-fold number	≥4-fold number	Initial	Post			≥2-fold number	≥4-fold number	Initial	Post	
Influenza A$_2$/Aichi											
Number:											
9	8 (88.9)	7 (77.8)	<10	37.0	≥7.4	12	11 (91.7)	10 (83.3)	<10	33.6	≥6.7
6	6 (100.0)	6 (100.0)	10	179.6	17.9	3	3 (100.0)	9 (33.3)	10	31.8	3.2
18	17 (94.4)	16 (88.9)	54.9	527.8	19.2	21	19 (90.5)	12 (57.1)	42.8	195.0	4.0
33	31 (93.9)	29 (87.9)	≥18.8	210.1	≥11.2	36	33 (91.7)	23 (63.9)	≥19.9	84.3	≥4.7
Influenza B/Mass											
Number:											
13	13 (100.0)	12 (92.3)	<10	75.8	≥15.2	17	16 (94.9)	15 (88.2)	10	40.6	≥8.0
6	6 (100.0)	6 (100.0)	10	226.2	22.6	4	4 (100.0)	4 (100.0)	10	56.6	5.7
14	12 (85.7)	9 (64.3)	34.5	215.4	6.2	15	7 (46.7)	5 (33.3)	45.0	105.5	2.3
33	31 (93.9)	27 (81.8)	≥12.9	144.0	≥11.2	32	27 (75.0)	24 (66.7)	≥12.6	62.3	≥4.9

[1] The vaccines used were subunit, Wyeth lot 75, 0.5 ml intramuscularly and whole, Wyeth Sharples, 1.0 ml subcutaneously; Spring, 1971.

NOTE.—Figures in parentheses are percent.

Table 34—*Antigenicity of Whole Virus and Subunit Vaccines in Adults From (Kasal, J. A., Progress Report to Bureau of Biologics)*[1]

Initial titer[2]	Lilly vaccine (whole)				Wyeth vaccine (subunit)			
	Seroconversion[3]		GM fold-rise		Seroconversion[3]		GM fold-rise	
	14 d	60 d	14 d	60 d	14 d	60 d	14 d	60 d
A$_1$/England/72								
10	39/60 (65)	43/60 (72)	7.4	10.0	30/46 (65)	30/46 (65)	11.3	10.0
10	14/15 (94)	13/15 (87)	8.6	11.1	17/25 (68)	18/25 (72)	8.2	9.2
10 [32.4]	6/22 (27)	6/22 (27)	≥2.1	2.6	[30.5] 16/28 (57)	17/28 (61)	≥4.7	≥4.6
Total [8.6]	59/97 (61)	62/97 (64)	≥5.7	≥7.5	[9.9] 63/99 (64)	65/99 (66)	≥8.1	≥7.8
B/Mass/71								
10	47/57 (82)	46/51 (81)	7.5	2.6	28/34 (82)	25/34 (74)	7.6	5.3
10	14/18 (78)	13/18 (72)	5.2	1.7	23/32 (72)	21/32 (66)	4.8	1.8
10 [28.2]	13/22 (59)	9/22 (41)	1.9	2.1	[29.8] 14/33 (42)	9/33 (27)	2.2	2.2
Total [8.4]	74/97 (76)	68/97 (70)	5.8	4.6	[11.3] 65/99 (66)	55/99 (56)	4.4	3.8

[1] The vaccines used were 700 CCA/Eng/72 and 300 CCA B/man/71; 0.5 ml intramuscularly; 2 weeks later, 500 CCA B/HK/72.
[2] [ ] GM titer ≥10.
[3] No. 4 fold or ≥rise/No. subjects (%).

Table 35.—*Protective Capacity of Whole Virus and Split Virus Vaccines Against Natural Challenge by an Epidemic of A2/Hong Kong Influenza From a Study of Ruben et al. (Ref. 24)*

Study population [1]		Clinical influenza			
Group	Number	Number observed	Number expected	Percent reduction	Significance
Unvaccinated	22,819	168			
Whole virus vaccinated	1,312	2	10	80	$p<0.05$
TNBP (split virus) vaccinated	1,791	6	11	54	$p=0.05$
All vaccines	3,103	8	23	65	$p \geq 0.01$

[1] The Study population was students, age 17 to 22 years. It is clear that when those individuals who received the whole virus (conventional) vaccine are removed from consideration, the protective effect of TNBP vaccine is only marginally significant.

Table 36.—*Protective Capacity of a Bivalent Vaccine in an Elderly Population Against Natural Challenge by an Epidemic of A/England/72 Influenza From a Study by Ruben et al. (Ref. 25)*

	Number of cases	Cases of influenza in		Attack rate, percent [3]	
		Vaccinees [2]	Nonvaccinees	Vaccinees	Nonvaccinees
Floor of home: [1]					
1	7	4 (2)	3 (0)	11	12
2	9	4 (0)	5 (2)	9	15
3	15	8 (3)	7 (1)	14	24
5	25	20 (2)	5 (2)	31	24
All	56	36 (7)	20 (5)	18	13
4	52	2 (1)	50 (9)	67	59

[1] Fourth floor not included in study. Since, through error, vaccine, was administered to only a small number of patients on that floor.
[2] Number in parentheses indicates number from whom influenza virus recovered.
[3] The number of days of fever (had no other symptoms) was significantly reduced ($p < 0.001$) in vaccinees as compared to controls, whether or not influenza.

The data in the studies cited indicate that this subunit or split-virus vaccine is adequately antigenic in persons with prior experience with influenza antigens or related antigens in the vaccine. As with the Parke-Davis vaccine, persons without such prior immunologic experience appear to require more than a single dose.

b. *Safety.* (1) *Animals.* Tests meet requirements; no data were presented.

(2) *Humans.* Several lots of Wyeth Laboratories vaccine as presently produced have been tested at the standard dose level, and at least one vaccine has been tested at a level of 6,400 CCA units of A and 4,800 CCA units of B. All these tests have shown an acceptably low (10 percent) rate of local and systemic reactions in adults. In a comparative trial of commercial vaccines by Barry et al. (Ref. 11), the Wyeth Laboratories product was demonstrated to produce a rate of local and systemic reactions similar to that of whole virus vaccines. Phillips et al. (Ref. 20) noted no local or systemic reactions in 33 children aged 5 to 9 years given varying intramuscular doses (0.25 ml, 0.5 ml, 1.0 ml) of bivalent vaccine containing 700 CCA units of antigen in 0.5 ml.

No severe reactions were reported in an addendum to the inital submission. Avian leukosis viruses have been tested for by the COFAL test.

Considerable information on the safety of Polysorbate 80 is included in the material from the Bureau of Biologics

c. *Benefit/risk.* See generic review.

d. *Labeling.* See generic review.

3. *Conclusions.* a. *Critique.* This vaccine has many characteristics in common with another subunit vaccine produced by Parke, Davis & Co. Antigenicity in seropositive subjects is adequate; the predominance of evidence indicates antigenicity comparable to that of whole virus vaccines in seronegative subjects. Most of the latter have been adults. A study conducted by the Bureau concluded that individuals without previous exposure to influenza virus or with low preinoculation antibody titers responded significantly

less will to this vaccine than to licensed whole virus vaccines. A number of the subjects in this study were children.

Because this product has been used for fewer years than whole virus vaccines, field experience and controlled studies coincident with natural challenge are limited. Although several efficacy trials have been completed, this vaccine has not yet been shown clearly to protect against disease. In one instance a marginally significant degree of protection against a homologous strain was shown, and in the other fever was shortened but illness not prevented by vaccine against a related but heterologous strain. It should be pointed out, however, that in the first study the attack rate was less than 1 percent, and in the second elderly subjects were studied, for whom there are few comparable data available for zonally purified whole virus vaccines. Thus, assumption of efficacy is largely based on the antigenicity of the vaccine.

b. *Recommendations.* (1) The total body of evidence, including that recently developed in the national dose-response trial of A/swine vaccines, indicates that split-virus vaccines are adequately antigenic in persons with appropriate prior immunologic experience. In the case of H_1N_1, and presumably B/HK antigens, these include most school-age children and older persons. In the case of the A/swine antigen, adequate response in persons under 24 years of age requires more than one dose.

The Panel recommends that this product be placed in Category I and that the license be continued, subject to labeling which clearly indicates the necessity for more than one dose under certain circumstances.

(2) Further efficacy trials should be designed and implemented by the manufacturer.

References

(1) Schild, G. C., M. Henry-Aymard, and H. G. Pereira, "A Quantitative, Single-radial-diffusion Test for Immunological Studies with Influenza Virus," *Journal of General Virology*, 16:231–238, 1972.

(2) Waldman, R. H. and W. J. Coggins, "Influenza Immunization: Field Trial on a University Campus," *Journal of Infectious Diseases*, 126:242–248, 1972.

(3) Knight, V., R. B. Couch, R. G. Douglas, and N. M. Tauraso, "Serological Responses and Results of Natural Infectious Challenge of Recipients of Zonal Ultracentrifuged Influenza A_2/Aichi/2/28 Vaccine," *Bulletin of the World Health Organization*, 45:767–711, 1971.

(4) Gwaltney, J. M., Jr., W. P. Edmondson of Subcutaneous, Nasal, and Combined Influenza Vaccination. I. Antigenicity," *American Journal of Epidemiology*, 93:472–479, 1971.

(5) Couch, R. B., R. G. Douglas, Jr., D. S. Fedson, and J. A. Kasel, "Correlated Studies of a Recombinant Influenza-Virus Vaccine. III. Protection Against Experimental Influenza in Man," *Journal of Infectious Diseases*, 124:473–480, 1971.

(6) Rosenberg, G. A., "Meningoencephalitis Following an Influenza Vaccination," *New England Journal of Medicine*, 283:1209, 1970.

(7) Eddy, T. S. and N. A. Davies, "The Effect of Vaccine on a Closed Epidemic of Hong Kong Influenza," *South African Medical Journal*, 44:214–216, 1970.

(8) Wenzel, R. P., J. O. Hendley, M. A. Sande, and J. M. Gwaltney, "Revised (1972–1973) Bivalent Influenza Vaccine; Serum and Nasal Antibody Responses to Parenteral Vaccination," *Journal of the American Medical Association*, 226:435–438, 1973.

(9) Stiver, H. G., P. Graves, T. C. Eickhoff, and G. Meiklejohn, "Efficacy of 'Hong Kong' Vaccine in Preventing 'England' Variant Influenza A in 1972," *New England Journal of Medicine*, 289:1267–1271, 1973.

(10) Barry, D. W., E. Staton, and R. E. Mayner, "Inactivated Influenza Vaccine Efficacy: Diminished Antigenicity of Split-Product Vaccines in Mice," *Infection and Immunity, 10:1329–1336, 1974.*

(11) Barry D. W., R. E. Mayner, D. Hochstein, et al., "Comparative Trial of Influenza Vaccines: II. Adverse Reactions in Children and Adults," *American Journal of Epidemiology*, 104:47–59, 1976.

(12) Barry, D. W., R. E. Mayner, E Staton, et al., "Comparative Trial of Influenza Vaccines: I. Immunogenicity of Whole Virus and Split Product Vaccines in Man," *American Journal of Epidemiology*, 104:34–46, 1976.

(13) Hall, C. E., M. K. Cooney, and J. P. Fox, "The Seattle Virus Watch. IV. Comparative Epidemiologic Observations of Infections with Influenza A and B Viruses, 1966–1969, In Families With Young Children," *American Journal of Epidemiology*, 98:365–380, 1973.

(14) Davenport, F. M., "Antigenic Enhancement of Ether-Extracted Influenza Virus Vaccines by A1PO $_4$," *Proceedings of the Society for Experimental Biology and Medicine*, 127:587–590, 1968.

(15) Neurath, A. R., J. T. Stasny, B. A. Rubin, A. K. Fontes, W. A. Pierzchala, F. P. Wiener, and R. W. Hartzell, "The Effect of Nonaqueous Solvents on the Quaternary Structure of Viruses: Properties of Haemagglutinins Obtained by Disruption of Influenza Viruses with tri(nbutyl) Phosphate," *Microbios*, 2:309–224, 1970.

(16) Cromwell, H. A., F. B. Brandon, I. W. McLean, Jr., and J. F. Sandusk, Jr., "Influenza Immunization: A New Vaccine," *Journal of the American Medical Association*, 210:1438–1442, 1969.

(17) Warburton, M. F., D. S. Jacobs, W. A. Langsford, and G. E. White, "Herd Immunity Following Subunit Influenza Vaccine Administration," *The Medical Journal of Australia*, 2:67–70, 1972.

(18) Brandon, F. B., C. D. Barrett, Jr., A. E. Hook, and G. O. Lease, "Human Febrile Response in Humans to Neuraminidase of A_2/-Aichi/68 and B/Mass/66 Influenza Viruses," *Proceedings of the Society for Experimental Biology and Medicine*, 138:47–51, 1971

(19) Neurath, A. R., F. L. Ruben, B. A. Rubin, R. W. Hartzell, and S. Wong, "Antibody Response in Humans to Neuraminidase of A_2/-Aichi/68 and B/Mass/66 Influenza Viruses (35829)," 138:47–51, 1971.

(20) Kasel, J. A., R. B. Couch, J. R. Six, and V. Knight, "Antigenicity of Licensed Whole Virion and Subvirion Influenza Vaccines in 'High Risk' Persons," *Proceedings of the Society for Experimental Biology and Medicine*, 151:742–747, 1976.

(21) Phillips, C. F., C. A. Phillips, W. E. Hodgkin, B. R. Forsyth, B. A. Rubin, and M. E. Geraghty, "Killed Subunit Influenza Vaccine in Children," *Pediatrics*, 52:416–419, 1973.

(22) Ruben, F. L and G. G. Jackson, "A New Subunit Influenza Vaccine: Acceptability Compared with Standard Vaccines and Antigenicity in Increasing Dosage," *Postgraduate Medical Journal*, 49:185–192, 1973.

(23) Ruben, F. L. and G. G. Jackson, "A New Subunit Influenza Vaccine: Acceptability Compared with Standard Vaccines and Effect of Dose on Antigenicity," *Journal of Infectious Diseases*, 125:656–664, 1972.

(24) Ruben, F. L., L. W. Akers, E. D. Stanley, and G. G. Jackson, "Protection with Split and Whole Virus Vaccines Against Influenza," *Archives of Internal Medicine*, 132:568–571, 1973.

(25) Ruben, F. L., F. Johnston. and E. J. Streiff, "Influenza in a Partially Immunized Age Population; Effectiveness of Killed Hong Kong Vaccine Against Infection with the England Strain," *Journal of the American Medical Association*, 230:863–866, 1974.

Review of Adenovirus Vaccines

Adenovirus Vaccine Manufactured by Parke, Davis & Co.

1. *Description.* Two adenovirus vaccines were at one time marketed by Parke, Davis and Company: (1) a bivalent vaccine containing adenovirus Types 3 and 7; and (2) a trivalent vaccine containing Types 3, 4, and 7. Neither has been produced for many years, although both are still licensed (the manufacturer makes the comment that "this product formulation has not been marketed for many years"). Most of the comments in this review apply equally to the bivalent and trivalent vaccines.

The manufacturer's description of the bivalent vaccine is as follows:

> Adenovirus Vaccine is an aqueous combination of inactivated adenoviruses, types 3 and 7, combined in approximately equal proportions. The viruses are propagated in tissue cultures of monkey kidney cells in a special nutrient medium (Synthetic Mixture No. 199). Inactivation of the viruses is accomplished by treatment with formaldehyde under controlled conditions, supplemented with ultraviolet irradiation and betapropiolactone. Phermerol (benzethonium chloride, Parke, Davis and Company) 1:40,000, is included as a preservative.

Further description of the bivalent vaccine is provided, but it does not

include any details on the manufacturing method. The basis for selection of the virus strain, and the methods for clarification or purification of the virus, for testing of preinactivation infectivity and potency testing are not given.

a. *Recommended use.* These vaccines, according to the package insert, are for prophylaxis of infection produced by adenoviruses Types 3 and 7, and a single injection of 1.0 cm ^{3}, administered intramuscularly or subcutaneously, is recommended for adults. The dosage for children has not yet been established, nor has the need for booster injections been determined.

b. *Contraindications.* The package insert states: "It is recommended that immunization be deferred in the presence of cerebral damage, active infections, or acute respiratory disease."

2. *Analysis.*

a. *Efficacy.*

(1) *Animals.* No data concerning tests of this product in animals were submitted. The literature records that the antigenicity of experimental adenovirus vaccines in guinea pigs is low (Ref. 1). Potency tests are required under 21 CFR 630.24. These necessitate testing each lot in comparison to a standard National Institutes of Health (Bureau of Biologics) vaccine and measuring the neutralizing antibody response. The animal(s) to be used in these tests is not specified.

(2) *Humans.* Data on the antigenicity in man of two bivalent lots and five trivalent lots were submitted and are summarized in Table 37.

Table 37.—*Antigenicity in Man of Bivalent and Trivalent Adenovirus Vaccines* [1], *Parke, Davis & Co.*

Clinical protocol	Vaccine lot	Serological response to vaccine: Number of persons with: Preimmunization titer >1:4			Postimmunization titer > 1:4			Percent of persons responding		
		Type 3	Type 4	Type 7	Type 3	Type 4	Type 7	Type 3	Type 4	Type 7
Bivalent vaccines										
371–1	024030	45		72	45		62	100		92
371–3	40184	7		13	7		14	100		93
Trivalent vaccines										
324	081291	17	30	26	16	26	24	94	87	92
	0854-96	23	30	29	22	26	23	96	87	79
371	B090877	26	50	10	19	16	7	70	50	70
	B090878	22	50	11	16	11	11	73	55	100
381	B090898	10	15	20	10	14	16	100	93	80
Total		148	125	163	125	95	157			
Percent								81	76	96

[1] Bivalent = type 3 and type 7 vaccine. Trivalent = type 3, 4 and 7 vaccine.

Protection data for the Parke, Davis & Co. product were not presented in the original submission, but were extensively reviewed by Parke, Davis & Co. representatives at the meeting of the review panel on April 2–3, 1974. The references cited are numerous. One concerns a hexavalent (Types 1, 2, 3, 4, 5, 7) Parke-Davis vaccine administered to 104 children, which was "moderately" antigenic; there was no change in the number and severity of respiratory illnesses in the year following vaccination as compared to the preceding year (Ref. 2).

In another trial, varying doses of what appears to have been the same vaccine induced greater than two-fold antibody responses in from 7 percent to 76 percent of 63 allergic children, 7 to 12 years of age, depending on dose and serotype. Protective efficacy of the vaccine was not reported (Ref. 3).

Gundelfinger, et al. (Ref. 4) studied a trivalent Parke-Davis vaccine in naval recruits. Twenty percent of the group received vaccine 3 to 5 days after arrival at the basic training installation. Rises in antibody to the vaccine viruses were found in 50 to 70 percent of the vaccines; adenovirus infections were, however, frequent in this population. The rate of reduction of febrile or hospitalized respiratory disease in vaccinees during the third to ninth weeks was calculated by the authors to be 65 percent. In addition, the rate of clinical viral pneumonia in the vaccinated population (0.04/1,000/week) was not significantly different from that in the control population (0.3/1,000/week, $p>0.1$).

Experience similar to this in other military studies has been reported many times with inactivated adenovirus vaccine, with protection rates as high as 90 percent for a Parke-Davis product (Ref. 5). The early studies, summarized by Hilleman suggest that the success of the vaccine depends to a large extent on its potency (Ref. 6).

Studies in the military are, because of the very nature of these groups, short-term, and no efficacy studies in adult civilian populations, or in military recruits, have been conducted over prolonged time periods.

b. *Safety.*

(1) *Animals.* Federal regulations outline the extensive testing required in animals in order to detect possible extraneous agents in adenovirus vaccines. These tests include the following examinations on the inactivated product: inoculation of tissue cultures, with subculturing for detection of SV–40; intracerebral inoculation of mice for lymphocytic choriomeningitis (LCM) land other mouse pathogens; tests (not specified) for *Herpes simiae* virus (B virus) and *M. tuberculosis*; identity tests; tests for live adenovirus; and monkey neurovirulence tests. The marketed vaccine has passed these tests.

The early lots of vaccine undoubtedly contained abundant SV–40 genetic material and, in some instances, low levels of infectious SV–40, since the component vaccine viruses were grown in primary rhesus monkey kidney cells. No comment on this contamination by an adventitious agent was made by the manufacturer in the original submission, but the problem was addressed in a presentation at the meeting of April 2–3, 1974, and changes which would eliminate the SV–40 problem were proposed in the manufacturing precedure.

(2) *Humans.* The vaccine produces few and mild local and systemic reactions. The manufacturer also submitted data on febrile reactions, and the extent of these is acceptable.

The major concern about adenovirus vaccines has been because of the possible oncogenicity for man of both the adenovirus and the SV–40 components. However, the inactivation methods in current use are adequate to eliminate the tumorigenicity of both adenovirus and SV–40 for hamsters, and, in addition, an extensive search failed to implicate adenoviruses in human cancer (Ref. 7). However, there is a lingering sense of uncertainity in the minds of many concerning the potential capacity of an adenovirus vaccine to produce tumors in man, whether or not it contains SV–40, and this uncertainty

must enter the benefit-risk ratio in some form.

The marketing data submitted stated some millions of doses of vaccine were sold between 1957 and 1964, and no major untoward reactions were reported.

c. *Benefit/risk.* The possible benefits of any adenovirus vaccine to the civilian population have never been demonstrated. The Panel found the presentation of the Parke-Davis group in this regard, and in particular there cost-benefit analysis, to be unconvincing. Indeed, there are statements in the literature which clearly express the view that adenovirus vaccines are not of value. Thus, Hilleman et al (Ref. 8) state that:

> * * * adult civilian groups, including families, university students, university employees, and selected cases of acute respiratory illness from hospitals or private practice, have shown very low attack rates for adenovirus-caused respiratory disease. Based on current information therefore general use of the [adenovirus] vaccine among such persons is not warranted and cannot be justified.

A similar conclusion comes from Jordan (Ref. 9):

> While the efficacy and desirability of administering adenovirus vaccine to military recruits has been established, the evidence cited indicates that such immunization of civilian populations, including university students and older adults, is not warranted.

The statement is made in the Parke-Davis submission that:

> Unregimented civilians are not ideal study groups and extended and detailed observations are required if the adenovirus contribution to the general etiology of respiratory illness is to be properly assessed. In spite of these logistic problems, a number of studies have been reported which attest to the ubiquity of adenovirus associated disease. While the figures from each of these reports can be considered valid only for the age group and geographical area studied, the epidemiological outline is clear. Five percent or more of significant civilian respiratory disease (increasing to perhaps 10 percent of children) can be attributed to endemic adenovirus infection with types 3 and 7.

Against this stands Brandt's huge survey among children in the Washington, DC area (Ref. 10) which showed that adenoviruses Types 3 and 7, respectively, were recovered from only 1.3 percent and 0.4 percent of 11,490 children with respiratory disease and 0.4 percent and 0.2 percent of 6,606 matched controls and that, of nearly 1,800 adenovirus isolates, the most numerous were Type 1 (26.3 percent) and Type 2 (34.5 percent), Type 5 (10.6 percent) followed by Type 3 (10 percent) and Type 7 (3.3 percent). Admittedly, virus recovery does not identify all actual infections, but it seems doubtful that the proportion of respiratory illness in children is as high as 10 percent. Indeed, using both virus recovery and antibody response, only 5.5 percent of respiratory illness in hospitalized children could be associated with all adenovirus types.

The recent report of Monto and Ullman (Ref. 11) was quoted extensively by the manufacturer to back his contention that adenoviruses (presumably, according to his argument, of the types included in the vaccine) cause 4.5 percent of respiratory illness in a community. The report, however, states that adenoviruses, all types, constituted 4.5 percent of specific agents isolated from respiratory illnesses. A viral or potentially pathogenic bacterial isolate was recovered from 24.9 percent of specimens. Thus, in the study cited, adenoviruses, including types not in the vaccine, were associated with about 1 percent of acute respiratory illnesses. This qualification makes the manufacturer's argument concerning the medical and economic need for his vaccine less than convincing.

Because of these considerations, it seems apparent that the benefits of a bivalent or trivalent adenovirus vaccine are very small or nonexistent. The risk may also be small, but it should be pointed out that the manufacturer's proposal for producing vaccines free of SV–40 and SV–40 genetic material have not been subjected to actual practical experience in either production or clinical testing. The label and package inserts are factually correct. Nevertheless, the experience quoted is that of early military trials, and hence the benefits implied are greater than those to be expected with the vaccine as used in the general population.

3. *Conclusions.*

a. *Critique.* The points at issue are:

(1) The presence of SV–40 and SV–40 genetic material in the vaccine as originally licensed during the period before SV–40 virus was discovered (the manufacturing process covered by the current license would not eliminate the presence of SV–40 genetic material);

(2) The untested feasibility of producing, by the manufacturer's proposed methods, vaccines free of SV–40 and SV–40 genetic material;

(3) The 10-year period since the last production;

(4) The lack of evidence of efficacy in the populations for which the vaccine is recommended by the manufacturer, namely civilian adults;

(5) The lack of efficacy data for any proposed "pediatric" formulation;

(6) The lack of data on the duration of protective effect;

(7) The doubtful need for a vaccine to prevent a very small (apparently less than 1 percent) proportion of respiratory disease;

(8) Because of (1), (2), and (6) above, the benefit/risk ratio is low or incalculable;

(9) The availability of live, orally administered vaccine for use in military populations.

b. *Recommendation.* Because of the issues raised in the critique above, the Panel believes that, based on considerations of effectiveness and need, the only justifiable use for such products would be for the prevention of respiratory disease in military recruit populations. Questions regarding the safety of these products, and the availability of other means for the control of adenovirus disease in such populations, weigh heavily against licensure even for such limited use.

The Panel recommends that this product be placed in Category II and that appropriate license(s) be revoked because there are compelling reasons to assume a lack of safety or effectiveness and an unsatisfactory benefit-risk ratio for this product.

Adenovirus and Influenza Virus Vaccine, Combined Manufactured by Parke, Davis & Co.

1. *Description.* According to the manufacturer's package insert:

Resprogen is a multivalent vaccine designed to immunize against both epidemic influenza and the more common adenovirus infections.

This vaccine is a sterile combination in 0.85 percent sodium chloride of two products adsorbed on an optimum amount (3.5 mg. per 1 cc. dose) of aluminum phosphate: Influenza Virus Vaccine, Polyvalent and Adenovirus Vaccine, Types 3 and 7. The color may vary from buff to a definite pink due to the residual organic indicator contained in the adenovirus vaccine component which is not entirely removed in the adsorption process.

Each 1.0 cc. contains the following strains of influenza virus propagated in developing chick embryos, concentrated and refined by ultracentrifugation and inactivated by ultraviolet irradiation:

Influenza Virus

Type	Strain	Conc. per ml.
A	PR 8	[1] 100 CCA
A1	Ann Arbor/1/57	100 CCA
A2	Japan/170/62[2]	200 CCA
B	Maryland/1/59	200 CCA
Total		600 CCA

[1] Chicken Cell Agglutinating Units.

[2] Asian Strain.

Each 1.0 cc. also contains adenoviruses types 3 and 7, in approximately equal antigenic proportions, which have been propagated in monkey kidney tissue cultures and inactivated with a combination of treatment with formaldehyde, ultraviolet irradiation and beta-propiolactone, as required. Thimerosal (mercury derivative), 0.01 percent, is used as a preservative. The combined vaccine meets all requirements of the National Institutes of Health as to safety and potency for both Influenza Virus Vaccine and Adenovirus Vaccine.

It is clear that the influenza virus component of the vaccine is made by an early protocol, according to which only modest efforts at purification were made. Details are not supplied.

a. *Recommended use.* As stated in the package insert, the objective of the vaccine is: "To immunize against both epidemic influenza and the more common adenovirus infections."

The package insert states that the recommended dose for adults 16 years of age and over is two intramuscular injections of 1.0 cm^3 each, given at least 2 months apart. "The dosage in children has not been firmly established." In individuals who have completed an immunizing course of injections, an annual booster dose is recommended prior to November 1.

b. *Contraindications* (as stated in the package insert).

When there is a history of allergy to egg proteins, chicken feathers or chicken dander, the use of products prepared from embryonic fluid of chicken eggs is contraindicated.

Resprogen contains small amounts of streptomycin used in culturing the adenovirus. During the adsorption process most of the antibiotic content is removed. However, consideration should be given to the possibility of allergic reactions in individuals sensitive to this antibiotic, and they should be tested for sensitivity where this possibility exists.

2. *Analysis.*

a. *Efficacy.*

(1) *Animals.* See adenovirus vaccine review above.

(2) *Humans.* The data supplied imply that the antibody response to the adenovirus component of the vaccine is the same as for that component alone (see adenovirus vaccine review). However, because the antibody elicited is measured in terms of percent conversion from <1:4 to >1:4, the degree of response cannot be compared. Similarily, the data supplied on response to the influenza virus component are not sufficient to judge the adequacy of the product (percent of vaccine recipients showing seroconversion from <1:5 to >1:5).

A report by Cox et al. (Ref. 12) records antibody responses engendered by several different adenovirus vaccines. The antigenicity of these several vaccines in terms of the seroconversion rate is summarized in Table 38.

Table 38.—*Seroconversion Rates (Neutralizing Antibody) Effected by 3 Different Adenovirus Vaccines Study of Cox et al. (Ref. 12)*

Adenovirus type	Seroconversion rate, percent, at 2 weeks postvaccination—Vaccine[1]			
	No. 1	No. 2	No. 3	Placebo
3	100	82	95	44
4	93	52	52	16
7	78	62	87	24

[1] Vaccine No. 1: Adenovirus types 3, 4, and 7. No. 2: Adenovirus types 3, 4, and 7 plus PR8, PR301, several influenza A viruses, and Great Lakes and Lee influenza B virus. No. 3: Same as vaccine 2, with aluminum phosphate adjuvant added. Vaccines were administered in 1.0 ml doses at 0, 16, and 52 weeks.

No controlled clinical trials for determining the capacity of such vaccines to protect against adenovirus disease have been reported.

Evidence for a protective effect conferred by the combined product is scanty. The literature contains only one study where a Parke-Davis manufactured adenovirus-influenza combination was tested for efficacy (Ref. 13). In this study the reduction in cases of influenza after immunization was similar between the groups receiving influenza vaccine alone, adeno-influenza vaccine or receiving adeno-influenza-para-influenza vaccine. However, statistical significance ($p=0.05$) in the reduction of morbidity was evident only when all three groups were combined (reduction 79 percent).

A mineral oil-arlacel adjuvant combined adenoinfluenza vaccine was found highly protective against both influenza and adenovirus disease in a military population (Ref. 14). Similarly, influenza and adenovirus vaccines administered simultaneously but as separate preparations have been shown to protect against both viruses, although in those studies only the influenza component was made by Parke, Davis and Company (Refs. 15 and 16).

b. *Safety.*

(1) *Animals.* See adenovirus vaccine review.

(2) *Humans.* See adenovirus vaccine review.

The reaction rates to this vaccine are higher than those quoted for adenovirus vaccine alone and are consistent with those seen in earlier years with less highly purified influenza vaccines. Thus, in one study, after a primary injection 28 percent noted local induration and/or erythema, 2 percent systemic reaction only, and 1 percent both. After a booster dose, 33 percent showed a local reaction, 11 percent fever and 7 percent both. In another study almost 50 percent noted a rise in temperature of more than 1° F at 24 hours.

The manufacturer's marketing experience states that several million doses were given in 1959–1965. "Very few complaints of reactivity, local or systemic, were received," but files have been discarded.

c. *Benefit/risk.* See adenovirus vaccine review.

d. *Labeling.* See adenovirus vaccine review. The labeling for the influenza component is not appropriate in the light of current standards.

3. *Conclusions.*

a. *Critique.* The same comments apply here as apply to the adenovirus vaccine. In addition, the influenza virus component has been produced by older methods, and some efficacy and antigenicity studies would be necessary with the combined product if the newer methods were used. It is doubtful, however, that this combined vaccine has any role in civilian medical practice, and its role in the military would be exceedingly limited, for the following reasons:

(1) The combination is not rational.

(i) Adenoviruses do not change in antigenic character.

(ii) Influenza viruses do change and would have to be changed with each substantial antigenic shift in the wild virus.

(2) The composition is inappropriate.

(i) Adenovirus types other than 3, 4, and 7 produce most of the infections and illnesses in civilian populations, particularly in infants and children.

(ii) Influenza antigens are deficient in amount by a factor of 5 to 10.

(3) The recommended usage is contradictory.

(i) Apart from military populations, and perhaps very few civilian groups, the target population for adenovirus vaccine is considered to be young children.

(ii) The target population for influenza vaccine is composed of adults, particularly those at high risk by reason of age or disease.

(4) The vaccine has not been made for some years.

(b) *Recommendation.* The Panel recommends that this product be placed in Category II and that appropriate license(s) be revoked because there are compelling reasons to assume a lack of safety or effectiveness and an

unsatisfactory benefit-risk ratio for this product.

References

(1) Hilleman, M. R., R. A. Stallones, R. L. Gauld, M. S. Warfield, and S. A. Anderson, "Prevention of Acute Respiratory Illness in Recruits by Adenovirus (RI-APC-ARD) Vaccine," *Proceedings of The Society For Experimental Biology and Medicine*, 92:377–382, 1956.

(2) Kozinn, P. J., H. Wiener, and J. J. Burchall, "Effectiveness of Adenovirus Vaccine in Children with Repeated Acute Respiratory Illness," *Journal of Pediatrics*, 59:669–673, 1961.

(3) Chobot, R., S. E. Goldzier, T. Schwartz, and D. Osborne, "Antibody Titer in Allergic Children Given Adenovirus Vaccine," *Journal of Allergy*, 30:97–102, 1959.

(4) Gundelfinger, B. F., M. J. Hantover, J. A. Bell, C. G. Loosli, and W. P. Rowe, "Evaluation of a Trivalent Adenovirus Vaccine for Prevention of Acute Respiratory Disease in Naval Recruits," *American Journal of Hygiene*, 68:156–168, 1958.

(5) Stallones, R. A., E. H. Lennette, R. E. Nitz, and A. H. Holquin, "Evaluation of an Adenovirus Vaccine in a Dispensary Population," *American Journal of Hygiene*. 72:100–110, 1960.

(6) Hilleman, M. R., "Adenovirus Vaccine: Development, Field Evaluation, and Appraisal of the Need for Vaccination in Military and Civilian Populations," *Archives of Internal Medicine*, 101:47–53, 1958.

(7) Truffelli, G. T., E. A. Timm, W. B. Beardmore, and I. W. McLean, Jr., "Inactivation of Adenovirus and Simian Virus 40 Tumorigenicity in Hamsters by Vaccine Processing Methods," *Applied Microbiology*, 15:516–527, 1967.

(8) Hilleman, M. R., J. H. Greenberg, M. S. Warfield, S. A. Anderson, and R. R. Glabere, "Second Field Evaluation of Bivalent Types 4 and 7 Adenovirus Vaccine," *Archives of Internal Medicine*, 102:428–436, 1958.

(9) Jordan, W. S. "Occurrence of Adenovirus Infections in Civilian Populations," *Archives of Internal Medicine*, 101:54–59, 1958.

(10) Brandt, C. D., H. W. Kim, A. J. Vargosko, B. C. Jeffries, J. O. Arrobio, B. Rindge, R. H. Parrott, and R. M. Chanock, "Infections in 18,000 Infants and Children in a Controlled Study of Respiratory Tract Disease. I. Adenovirus Pathogenicity in Relation to Serologic Type and Illness Syndrome," *American Journal of Epidemiology*, 90:484–500, 1969.

(11) Monto, A. S., and B. M. Ullman, "Acute Respiratory Illness in an American Community. The Tecumseh Study," *Journal of the American Medical Association*, 227:164–169, 1974.

(12) Cox, F. C., Jr., E. A. Timm, E. L. Quinn, J. M. Colville, and I. W. McLean, "Acute Respiratory Infections in Civilian Adults: I. Antibody Response to Polyvalent Influenza—Adenovirus Inactivated Vaccine," *Henry Ford Hospital Medical Bulletin*, 10:27–33, 1962.

(13) Cox, F. Jr., E. A. Timm, I. W. McLean, C. F. Weiss, and E. L. Quinn, "Acute Respiratory Infections in Civilian Adults. II. Clinical and Serologic Observations in a Vaccine Study Group," *Henry Ford Hospital Medical Bulletin*, 11:273–278, 1963.

(14) Meiklejohn G., "Adjuvant Influenza Adenovirus Vaccine," *Journal of the American Medical Association*, 179:594–597, 1962.

(15) Schultz, I., W. T. Stille, B. F. Gundelfinger, and L. F. Miller, "Combinations of Asian Influenza Virus and Adenovirus Vaccine in the Prophylaxis of Respiratory Illness of Navy Recruits, (Part I)," *American Journal of Public Health*, 50:543–550, 1960.

(16) Stille, W. T., I. Schultz, B. F. Gundelfinger, and L. F. Miller, "Combinations of Asian Influenza Virus and Adenovirus Vaccine in the Prophylaxis of Respiratory Illness of Navy Recruits, (Part II)," *American Journal of Public Health*, 50:275–289, 1962.

Review of Rabies Vaccine

Rabies Vaccine (Duck Embryo), Dried Killed Virus Manufactured by Eli Lilly & Co.

1. *Description.* The vaccine is a dried suspension of duck embryo tissue infected with fixed rabies virus, which is inactivated with beta-propiolactone; 1:10,000 merthiolate is used as a preservative. The claim is made that the vaccine contains little or none of the "paralytic factor" (presumably myelin) responsible for posttreatment paralysis associated with vaccine of central nervous system origin. The vaccine is stated to meet potency requirements as measured by the National Institutes of Health mouse potency test, and to induce antibodies detectable by the 10th (often) to the 15th day (nearly always) after initiation of the standard series of 14 daily doses.

a. *Recommended use.*

(1) *Risk.* The risk of fatal disease is a compelling basis for use. The argument against giving rabies vaccine unless actual exposure has occurred relates to posttreatment paralysis, which is said to be minimal with duck embryo vaccine. While the bite of an animal known to be rabid results in approximately a 40 percent risk of rabies, little or no risk follows unless there has been an actual lesion or abrasion made by the animal.

Current ACIP procedures for postexposure prophylaxis are recommended, including the prescribed use of antiserum or human antirabies immunoglobulin.

Since there is a suppressive effect of antibody on active response to vaccine, it is recommended that additional doses of vaccine be given at 10 and 20 days after the last usual dose of the series in order to counteract this effect.

Consultation with local health officials about the prevalence of rabies in a given region is advisable before any decision to use vaccine is made. Preexposure immunization is recommended for specified high risk groups.

(2) *Local treatment.* The recommendations of the WHO should be followed, including, if antibody is to be given, infiltration of antiserum or immune globulin around the site of the bite-wound.

(3) *Prognosis.* It has been suggested that postexposure vaccination is most likely to be effective when the incubation period is expected to be more than 3 or 4 weeks; this interval is usually estimated on the basis of the severity and location of the lesion.

With severe exposure, shorter incubation is expected and vaccine failure is more likely, but by no means certain, and hence prompt initiation of therapy is considered essential.

(4) *Dosage and administration.*

(i) *Postexposure.* the minimum course consists of 14 inoculations over a 14-day period. The vaccine is administered subcutaneously over the abdomen; alternate slides are injected each day and a different site used for each dose. A site previously employed for another vaccine or toxoid should not be used.

Because reactions to the vaccine are minimal, and early development of antibody is important, it is suggested that vaccination be inititated promptly in cases of bites to the head, neck, or arm inflicted by a healthy appearing animal (rather than withholding vaccine for up to 10 days if the animal remains healthy) and discontinue administration after 5 days if the animal is still healthy, pending further observation.

In the cases of bites by wild animals (risk of rabies is higher and incubation period may be short), the suggested regiment involves 2 doses of vaccine each day for 7 days and then 7 single daily doses (total 21 doses). Also, the ACIP recommends that if antibody is used, supplemental doses of vaccine should be given at 10 and 20 days after the last dose of the course.

(ii) *Preexposure immunization.* Two equally effective regimens are described: (1) four doses of 1 ml each, three at weekly intervals and the fourth 5 or 6 months later; (2) three doses of 1 ml each, the second after 1 month and the last 7 months later. Either regimen should elicit demonstrable neutralizing antibody levels in over 80 percent of subjects one month after the final dose. While antibody persistence and the frequency with which booster inoculations are required are not known, it is suggested that persistence of immunity could be assured by periodic (every year or two) 1 ml boosters.

Since an antibody response is not consistently induced, the antibody titer must be determined after a course of

vaccine; (appropriate serum specimens may be sent to the CDC via the local health agency). If no antibody is found, additional doses of vaccine should be given until a response is elicited.

Should mild exposure subsequently occur in persons who do develop antibody, only a single 1 ml booster dose of vaccine is needed. Following severe exposure, five daily doses of vaccine and a booster dose 20 days later should be given.

b. *Contraindications.*

(1) *Precautions.* Use of this vaccine should be avoided in individuals with a history of allergy to chicken or duck eggs or proteins.

The use of steroids postexposure is to be avoided, as these may lower resistance to infection and suppress the antibody response, thereby possibly causing an apprent vaccine failure.

Pregnancy is no contraindication if exposure conditions dictate use of the vaccine.

(2) *Adverse reactions.* Local reactions are common, and later injections in the series may cause flare up in the sites of earlier inoculations; however, these are less frequent and less severe than those associated with nerve tissue vaccine (NTV), a product no longer licensed for manufacture in the United States.

Because the vaccine is a foreign protein, systemic sensitivity to its components may be encountered. Urticaria, respiratory distress (with dyspnea and bronchospasm), abdominal cramps, and nausea have occurred and anaphylactic reactions have been reported. Epinephrine may be helpful in such situations.

Constitutional reactions to the vaccine are difficult to evaluate (patients tend to be apprehensive), but the development of fever, malaise and drowsiness calls for careful observation. Minor neurologic reactions (headache, photophobia, paresthesias, and fatigability) have been reported and major reactions (transverse myelitis, cranial or perepheral palsy, and encephalitis) have been reported rarely. Vaccination should be discontinued if neurologic symptoms develop.

2. *Analysis.*—a. *Efficacy and safety.* The 1972 report of the ACIP states that in the United States, comparative effectiveness can be judged only by reported failures. During 1957 to 1971, there were 6 failures in 125,000 persons treated with NTV for a failure rate of 1:20,800, compared with 12 failures in 310,000 individuals given duck embryo vaccine (DEV) or a failure rate of 1:25,800.

Since these failure rates are not appreciably different, DEV is preferable because of its greater safety.

(1) *Recommendations from the medical literature.* Greenberg and Childress (Ref. 1) reported on 123 persons given DEV and 127 given NTV (Semple type). Duck embryo vaccine induced an earlier antibody response and no CNS reactions as compared with two cases of encephalomyelitis in the NTV group. Both vaccines proved effective boosters in previously immunized individuals. Their findings support the replacement of NTV by DEV.

Powell and Culbertson (Ref. 2) found that DEV protected rabbits against challenge with virus and, in man, induced antibody which neutralized both fixed and street virus.

Rubin et al. (Ref. 3) reviewed retrospectively adverse reactions to DEV used in the United States. Between 1958 and 1971, 42 1,000 persons had received courses of DEV. A fatal encephalitis developed in two of these, almost certainly rabies in each case, but there was insufficient diagnostic information to be certain. A nonfatal encephalopathy appeared in two others, transverse myelitis in four and cranial and/or peripheral neuropathy, reversible with (steroid) treatment, in five. Thus no fatalities could be attributed with certainty to the DEV, and major neurologic disease was rare and, in general, reversible.

In the same survey, Rubin et al. (Ref. 3) reported 22 instances of anaphylaxis, more than half of which could not be predicted even in retrospect from a history of allergy, etc. However, they noted that prior to their rabies immunization, some of these individuals had received several vaccines containing agents grown in avian tissues.

These authors also reported on a prospective study on the postexposure treatment of 116 individuals and recorded local discomfort in 100 percent of instances, constitutional symptoms during therapy in 33 percent, and anaphylaxis in 0.9 percent. They noted that the figure of 0.5–0.9 percent anaphylaxis is significant, inasmuch as the rate of anaphylaxis associated with administration of penicillin is 0.015–0.4 percent.

Tierkel and Sikes (Ref. 4) reported that giving DEV in a three dose regimen (0, 1, and 8 months) induced antibody in 90 percent of their volunteers.

(2) *Potency testing.* The official United States test for the potency of rabies vaccine is the National Institutes of Health mouse potency test (Ref. 5). Each production lot is compared with the United States reference rabies vaccine and must show a potency ratio of at least 0.3 times this reference standard in order to obtain approval for release by the Bureau. Manufacturing records indicate a rejection rate (failure of potency) of from 3 percent to 10 percent of lots, depending on which reference vaccine was used.

b. *Safety.* See Efficacy above.

c. *Benefit/risk.* The gravity of rabies is such that any vaccine which possesses a fair measure of efficacy, and is virtually nonlethal itself, warrants a favorable ratio.

d. *Labeling.* This should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to updated recommendations of ACIP. The hazard of anaphylaxis should be stressed since this is the most prominent potential reaction to DEV.

3. *Conclusions.*—a. *Critique.* (1) *Efficacy aspects.* Duck embryo vaccine is the only rabies vaccine now available. For obvious reasons, no trails of true efficacy are possible (prevention of rabies by either postexposure therapy or preexposure prophylactic immunization) so that one must rely on ability to induce neutralizing antibody in man as an index of efficacy.

The Advisory Committee on Immunization Practices recommendations urge that rabies antibody be used in postexposure prophylaxis; such administration of immune serum or human rabies immune globulin inhibits an active immune response by the patient. Experience suggests that such inhibition is especially marked with DEV (Refs. 6 and 7).

While there are data indicating that supplementary doses of vaccine 10 and 20 days later (the so called 16-dose course) are adequate to induce an active response after HRIB (Ref. 8), more recent data (Ref. 9) indicate that reliable induction of active response after HRIG requires a 23-dose course of DEV (daily for 21 days and again after 10 and 20 more days). Still more recent data from the CDC, presented to the Panel in June of 1974, indicated that satisfactory response was achieved more reliably in children under age 16 than in adults.

The relative safety of DEV as compared with NTV (see next section) made it possible to consider its use for preexposure immunization in high risk populations. The responses elicited with the regimens recommended are hardly satisfactory and further testify to the inadequate potency of DEV.

(2) *Safety aspects.* Duck embryo vaccine consists of crude embryo extracts containing beta-propriolactone (BPL) inactivated rabies virus. On a comparative basis, it is clearly safer

with respect to allergic CNS sequellae than is NTV. This is supported by data from animal studies and by experience in man.

However, DEV still leaves much to be desired. First, it is not completely devoid of the so-called paralytic factor; second, it contains an abundance of extraneous foreign protein with a demonstrated capability for inducing a variety of allergic reactions; and third, an effort should be made to detect and eliminate (if present) extraneous microorganisms, including avian reticuloendotheliosis viruses that may be present in duck cell substrates. Treatment with BPL plus merthiolate renders any such agents nonviable, but undesirable residual genetic viral material, if present, may persist.

Clearly, there is a need for a new product, one free of extraneous agents and with a greatly reduced proportion of extraneous protein. It is hoped that one of the cell culture vaccines still under study may resolve this situation.

Two such cell-culture vaccines were being studied at the time this report was prepared. Work has stopped on one, a vaccine utilizing virus grown in a baby hamster kidney cell line (BHK), which had excellent antigenic potency and apparent postexposure efficacy in rhesus monkeys (Ref. 10). It has the major theoretical drawback of derivation from a cell line rather than a cell strain or primary cell cultures.

The second tissue culture vaccine, using diploid WI–38 cells for viral propagation, has excellent antigenic potency and exceeds that of DEV by at least a factor of five, in addition to being a much cleaner product. However, recent unpublished data indicate that when it is used for long postchallenge protection of monkeys in an experiment similar to that with the BHK vaccine above, no certain protective effect could be shown (Ref. 13). Very recent preliminary data suggest that it can be used effectively in conjunction with antibody. This vaccine also has been tested on man for preexposure immunization; a three-dose regimen (0, 7, 21 days) induced response in 100 percent of vaccines with antibody levels 10-fold higher than induced by an optimal (0, 1, 6 months) regimen of DEV.

It should be noted that the immunologic phenomena involved in both protection against, and the pathogensis of, rabies are only poorly understood. In particular, recent work with rabies-related rhabdo-viruses and with rabies virus itself has yielded results which are contrary to what might be expected on the basis of classical concepts of immunity and which require further fundamental studies for adequate explanation (Refs. 11 and 12). As examples, immunosuppressed animals (mice) survive longer after challenge inoculation than do normal animals; delayed postchallenge administration of antibody to either immunosuppressed or to normal animals accelerates a lethal outcome; and animals immunized with rabies-related viruses (Lagos bat virus or Mokola virus) develop "neutralizing" antibodies to rabies virsus but are not only not protected against challenge with rabies virus but also die earlier than do controls (Refs. 10 and 11). Along this same line is the early death phenomenon noted by Sikes and other workers and illustrated by data on the postchallenge use of DEV in the mouse foot-pad model; not only did DEV fail to protect mice but the treated animals died earlier (significantly so) than did the untreated controls (Ref. 13).

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Every effort should be made to encourage the development of a better vaccine. However, DEV should be reviewed again when (and if) a new product is licensed. Furthermore, this generic product should be reviewed frequently as new information about rabies immunity and pathogenesis is developed in animal model systems. Basic research in these areas is obviously required in view of the uncertain basis for presently recommended procedures for immunoprophylaxis.

References

(1) Greenberg, M. and J. Childress, "Vaccination Against Rabies with Duck-Embryo and Semple Vaccines," *Journal of the American Medical Association*, 173:333–337, 1960.

(2) Powell, H. M. and C. G. Culbertson, "Action of Rabies Vaccine Derived from Embryonated Duck Eggs Against Street Virus," *Proceedings of the Society for Experimental Biology and Medicine*, 101:801–803, 1959.

(3) Rubin, R. H., M. A. Hattwick, S. Jones, M. B. Gregg, and V. D. Schwartz, "Adverse Reactions to Duck Embryo Rabies Vaccine: Range and Incidence," *Annals of Internal Medicine*, 78:643–649, 1973.

(4) Tierkel, E. S. and R. K. Sikes, "Preexposure Prophylaxis Against Rabies," *Journal of the American Medical Association*, 201:911–914, 1967.

(5) Seligmann, E. B., Jr., "The NIH Test for Potency," in "Laboratory Techniques in Rabies," Edited by M. M. Kaplan and H. Koprowski, World Health Organization Monograph Series No. 23:279–286, 1973.

(6) Archer, B. G. and R. E. Dierks, "Effects of Homologous or Heterologous Antiserum on Neutralizing-Antibody Response to Rabies Vaccine," *Bulletin of the World Health Organization*, 39:407–417, 1968.

(7) Ellenbogen, C. and P. Slugg, "Rabies Neutralizing Antibody: Inadequate Response to Equine Antiserum and Duck-Embryo Vaccine," *Journal of Infectious Diseases*, 127:433–436, 1973.

(8) Loofbourow, J. C., V. J. Cabasso, R. E. Roby, and W. Anuskiewicz, "Rabies Immune Globulin (Human): Clinical Trials and Dose Determination," *Journal of the American Medical Association*, 217:1825–1831, 1971.

(9) Hattwick, M. A. W., R. H. Rubin, S. Music, R. K. Sikes, J. S. Smith, and M. B. Gregg, "Postexposure Rabies Prophylaxis with Human Rabies Immune Globulin," *Journal of the American Medical Association*, 227:407–410, 1974.

(10) Sikes, R. K., W. F. Cleary, H. Koprowski, T. J. Wiktor, and M. M. Kaplan, "Effective Protection of Monkeys Against Death from Street Virus by Post-Exposure Administration of Tissue-Culture Rabies Vaccine," *Bulletin of the World Health Organization*, 45:1–11, 1971.

(11) Tignor, G. H., R. E. Shope, R. K. Gershon, and B. H. Waksman, "Immunopathologic Aspects of Infection with Lagos Bat Virus of the Rabies Serogroup," *Journal of Immunology*, 112:260–265, 1974.

(12) Tignor, G. H., R. E. Shope, P. N. Bhatt, and D. H. Percy, "Experimental Infection of Dogs and Monkeys with Two Rabies Serogroup Viruses, Lagos Bat and Mokola (IbAn 27377): Clinical, Serologic, Virologic, and Fluorescent-Antibody Studies," *Journal of Infectious Diseases*, 128:471–478, 1973.

(13) Baer, G. M. and W. F. Cleary, "A Model in Mice for the Pathogenesis and Treatment of Rabies," *Journal of Infectious Diseases*, 125:520–527, 1972.

Review of Yellow Fever Vaccine

Yellow Fever Vaccine Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell Inc.

1. *Description.* This is the only yellow fever vaccine licensed in the United States. According to the package insert, it is prepared by growing the 17D strain of yellow fever virus in living chick embryos. The vaccine is frozen, dried, and hermetically sealed under nitrogen in glass ampoules. No preservative is added. The product is a 75-percent suspension of embryos (by weight) in distilled water and is to be reconstituted in five volumes of diluent immediately before use.

The vaccine satisfies the potency and other requirements of the Public Health Service (PHS) and the World Health Organization (WHO).

a. *Recommended use.* (1) *Indications.* The vaccine provides active immunity against yellow fever for travelers visiting countries requiring a certificate of vaccination against this disease. Immunization is required of all individuals over 6 months of age.

(2) *Administration and dosage.* Rehydrate the contents of the ampoule

with the diluent provided, as directed. Shake well, withdraw the contents, and administer 0.5 ml subcutaneously (the dosage is the same for adults and children).

Immunity develops by the seventh day and lasts for many years, but revaccination is required after a lapse of 10 years.

(3) *Special note.* The vaccine retains its potency for at least 12 months if kept in the freezing compartment of a refrigerator. After reconstitution, it should be kept cool and used within 60 minutes. Yellow fever vaccine is available only at officially designated Yellow Fever Vaccination Centers, which are authorized to issue valid certificates of vaccination.

Production and distribution of the vaccine is under the strict control of WHO and PHS.

b. *Contraindications.* Proved or known sensitivity to egg or chick embryo protein is generally a contraindication. Except in high risk areas, pregnant women and infants under 6 months of age should not be vaccinated.

Abnormal immune states (leukemia, lymphoma, generalized malignanacy, and lowered resistance from therapy with steroids, antimetabolites, and radiation) may potentiate vaccine virus infection, and thus consittute a contraindication to vaccination.

(1) *Precautions.* If hypersensitivity to egg proteins is suspected, a skin test should be done with 0.02 ml of vaccine (a tourniquet and epinephrine solution should be immediately available). If uncertainty prevails, intradermal vaccination by the scratch method might be undertaken.

If other live virus vaccines are to be given, they should precede or follow the yellow fever vaccine administration by at least 1 month.

(2) *Adverse reactions.* Fever and/or malaise occurs in 10 percent of the recipients of the vaccine. Encephalitis has occurred, although rarely, in very young infants and usually without sequellae (one death has been reported).

2. *Analysis.* Two types of live virus yellow fever vaccine exist, and both are recognized as acceptable by WHO. The so-called Dakar vaccine, made with mouse passage-adapted "French Neurotropic" strain of virus, is definitely encephalitogenic in man (0.5 percent incidence) and is not recommended by ACIP nor is it licensed in this country.

The other type, produced in chick embryos infected with the 17D strain of virus, is represented by the Merrell-National product, which is the only yellow fever vaccine licensed in the United States (although similar vaccine is produced in other countries). The history of 17D vaccine is interesting and lengthy but only partly relevant to this review.

Wild yellow fever virus is both viscerotropic (in this instance with specific reference to liver disease) and neurotropic. Brief intracerebral passage in mice predictably results in loss of viscerotropism (as shown in rhesus monkeys, which provide an excellent, sensitive model which reflects the disease seen in man). However, neurotropism is retained and, at least for mice, is enhanced as evidenced by a markedly shortened incubation period. The Dakar vaccine is made with virus of this type. Max Theiler and coworkers undertook to develop a strain attenuated for neurotropism as well as viscerotropism by serial propagation of the virus in various types of tissue culture. The 17D line in tissue cultures of chick embryos, from which the CNS tissue had been removed, eventually (passage number 114) satisfied their criteria (negligible disease in intracerebrally inoculated rhesus monkeys) and was shown to produce a safe and effective vaccine for human use. This change proved not to be reproducible, at least at will, although simple passage in intact chick embryos has resulted in a 17D-like virus on one or two occasions.

Since 1937 17D vaccine, produced in chick embryos, has been used on an increasing scale, first in Latin America, and soon on a worldwide basis. In these early years, multiple parallel passages of 17D virus were maintained in tissue culture in different laboratories and often in the same laboratory. Vaccine lots were produced as needed from the then current passage level of these sublines. By 1943, three significant problems had been encountered.

First, failures of the vaccine to immunize were observed. These failures were referable to vaccine lots produced from virus at a very high subculture level (350th passage). Such virus, as was later shown, had become poorly infective for man, although it still poduced lethal encephalitis in cerebrally inoculated mice. This problem was resolved by reverting to earlier passage virus for vaccine production.

Second, a vaccine-associated encephalitis was observed in a few Brazilian children. Review of the testing experience in the yellow fever laboratory in Brazil, where various parallel passage lines of virus were used to make vaccine, revealed that the cumulative occurrence rate of encephalitis in monkeys inoculated with different production lots of vaccine differed appreciably according to the culture passage line used to produce the vaccine (Ref. 1). The significance of this finding was confirmed in large-scale field studies including a carefully controlled trial of vaccines produced from each of five 17D substrains (Ref. 2). This basic problem (and that of diminishing immunogenicity) was resolved by selecting, for production of a master seed lot, the safest substrain at the passage level at which it was employed in the field trial. Secondary seed lots to be used for inoculating producion lots, were prepared from this master seed lot, thereby permitting vaccine production within the confines of a narrow range of passages.

The third problem (chronologically, the second) was the occurrence of serum hepatitis in vaccine recipients. The occurrence of vaccine-associated hepatitis was first recognized in Brazilian populations by Fox et al. (Ref. 3) and later, on a much larger scale, in United States military personnel. The cause was "normal" human serum (heat inactivated at 56° C) incorporated into the vaccine as a source of "innocuous" protein to facilitate lyophilization and subsequent rehydration of the vaccine and to stabilize the vaccine virus once reconstituted. The solution was to omit the serum and to increase the concentration of embryo tissue (fluid) in the final product, thereby providing a protein concentration adequate for lyophilization and virus stability.

A fourth problem did not become apparent until the recognition of avian leukosis virus (ALV) and its almost universal presence in chick embryos. The resolution of this problem is theoretically simple but has proven more difficult in practice. Although a careful follow up study in the United States military did not show any association between human malignancies and yellow fever vaccination, it is clearly desirable to eliminate this extraneous virus (Ref. 4). This has apparently been accomplished in two ways. Draper succeeded by combining neutralization of ALV with passage by the limiting dilution technique whereas Tarauso, et al. achieved separation of the two viruses through graded filtration (Refs. 5 and 6). The resulting 17D virus, free of ALV, was used to produce vaccine seed material which, according to tests reported by them, did not differ from the seed of origin in terms of antigenicity and neurovirulence in monkeys or in immunogenicity and reactogenicity in man (Refs. 7, 8, and 9). On the basis of these findings, this ALV-free seed was judged acceptable by WHO.

In the United States, efforts are in progress to prepare a similar ALV-free seed virus for use in future production of yellow fever vaccine in this country.

The second effort at eliminating ALV from yellow fever was carried out earlier in the Division of Biologics Standards, but it has been found to be unsatisfactory for reasons discussed below.

a. *Efficacy.* The information available in the submission refers only to experience with the original ALV-contaminated vaccine. Extensive worldwide experience with this product, and the similarly derived vaccines produced elsewhere in the world, is highly reassuring with respect to both safety and effectiveness.

The 17D strain is derived from the wild Asibi strain, which is recovered from a Nigerian with a mild attack of yellow fever. In the course of its extended passage in chick embryo tissues, this strain has undergone minor (subtle) change in antigenic character but apparently remains adequately immunogenic against wild yellow fever strains. A review of vaccination experience through 1954 (cited in WHO Monograph No. 30, 1956) indicates that the only significant problem was in infants under 6 months of age, among whom several cases of encephalitis (all with full recovery) occurred.

The only version of the Division of Biologics Standards (Bureau of Biologics) minimum requirements is dated May 18, 1949 and agrees basically with WHO requirements. Production lots are tested for potency (at least 1,000 mouse MLD per dose), safety in guinea pigs, and sterility.

Only the primary and secondary seed lots are tested (all intracerebrally) in monkeys for neurovirulence, circulating virus (index of some retained viscerotropism), and immunogenicity. Merrell-National received the primary seed from PHS in 1952 and has had occasion to produce only three secondary seed lots, which were tested by the Division of Biologics Standards.

Since 1968, several million doses of vaccine have been distributed. A small number of reactions, often of dubious relation to vaccination, have been reported. These included one instance of encephalitis and one death which, after careful autopsy, could not be attributed to the vaccine.

b. *Safety.* See Efficacy above.

c. *Benefit/risk (of ALV-contaminated vaccine).* On the basis of human experience, the 17D vaccine is effective and minimally reactogenic, hence benefit far outweighs demonstrated risk. The known presence of ALV, however, is an undesirable factor of potential, but not yet established, risk.

d. *Labeling.* Since this vaccine is distributed only to officially designated centers, labeling is less important than for commercially available products; however, it is generally adequate. The time of expected acute reactions is not indicated and the possibility that use of the vaccine as a skin test antigen may in fact be immunizing is not considered. In a 1943 report of a vaccine trial in Brazil, data are presented indicating that intradermal inocula containing as little as 10 $TCID_{50}$ of virus induced immunity in all vaccinees (Ref. 9).

3. *Conclusions.*—a. *Critique.* One major problem, not considered previously, requires mention here, viz., no ALV-free vaccine has yet been licensed in this country. This situation exists because (1) the only manufacturer of ALV-free vaccine has not sought a license and (2) the ALV-free seed material produced by the former Division of Biologics Standards has been retested in monkeys by the Bureau of Biologics and found wanting (and also, in effect, by Merrell-National and two or three foreign laboratories). The reasons for this failure to conform the previously reported observations are not clear but may reflect more rigorous and uniform criteria for examining the test animals.

Information obtained during a briefing (March 18, 1974) by Dr. David Barry and others of the Bureau of Biologics indicates that the most important problem is an increased neurovirulence for monkeys, manifested by a clinically severe or fatal encephalitis in 6 of 24 animals (25 percent) and transient weakness in 3 others. Five monkeys died or were killed when moribound. In comparison, only one of 12 animals given the old (ALV-contaminated) seed showed evident weakness and developed severe (but nonfatal) disease. Thus, the new material (two seed lots, one primary and one secondary) failed to pass WHO requirements for neurovirulence. One new seed lot, together with the old seed, also failed to manifest adequate viscerotropism as reflected by viremia detected in mice. However (suggesting that viscerotropism is not a relevant criterion), all lots were highly immunogenic in monkeys. The Brazilian experience, which is not likely to be reproduced suggests that monkey neurovirulence is a valid marker for human risk. While Tauraso et al. (Ref. 10) observed no significant clinical reactions in a limited number of volunteers, the group was probably too small to give conclusive findings and probably too old (all were young adult males) to be sensitive detectors (young children have generally been more prone to give reactions). Thus the problem with the Division of Biologics Standards seed must be accepted as real, and it has both practical and theoretical implications.

On the practical side, the Bureau of Biologics must decide what vaccine should be immediately available in the United States. That now being produced (ALV-contaminated) is "safe" with respect to neurovirulence. Furthermore, Waters et al. (Ref. 4), in their study of cancer mortality among army veterans of World War II in relation to their immunization against yellow fever (ALV-contaminated vaccine), found no evidence that such vaccination had influenced the risk of subsequent malignancy 5 to 22 years later. Thus, it is probable that the presence of ALV is inconsequential. However, it is clearly desirable that vaccines contain no adventitious agents.

The possibility exists that yellow fever virus may have acquired ALV genetic material during the long period of concomitant passage. Hence, even though ALV-free strains of 17D virus are obtained which prove satisfactory with respect to the desired vaccine characteristics, it would seem prudent to explore this possibility.

Efforts by the Bureau of Biologics staff to modernize testing of the vaccine are to be commended. These changes involve: (1) substitution of plaque assay for mouse LD_{50} assay at all levels; (2) revision of criteria of immunogenicity in monkeys (e.g., substitution of parenteral for intracerebral routes of inoculation); (3) efforts to develop shorter and more reliable neurovirulence testing markers in monkeys; and (4) deletion from animal potency and safety testing of criteria involving viremia.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. The availability of a safe and effective yellow fever vaccine produced in the United States must continue. Steps to exclude ALV contamination should be taken as quickly as possible without jeopardizing the safety of the yellow fever virus strain employed. During the interval required to achieve this, the present vaccine should be maintained in use. By whatever means necessary, the Bureau should move to insure that ALV-free vaccine is made available in the United States. If necessary, this effort should include participation by the Bureau's staff in the research that will

most rapidly lead to development of a new ALV-free seed for acceptable neurovirulence. Modern virologic technology, including virus cloning and genetic studies, will be important in this program.

References

(1) Fox, J. P. and H. A. Penna, "Behavior of 17D Yellow Fever Virus in Rhesus Monkeys; Relation to Substrain, Dose, and Neural or Extraneural Inoculation," *American Journal of Hygiene,* 38:152–172, 1943.

(2) Fox, J. P. and E. H. Lennette, C. Manso, and J. R. Souza Aguiar, "Encephalitis in Man Following Vaccination with 17D Yellow Fever Virus," *American Journal of Hygiene,* 36:117–142, 1942.

(3) Fox, J. P., C. Manso, H. A. Penna, and M. Para, "Observations on the Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever," *American Journal of Hygiene,* 36:68–116, 1942.

(4) Waters, T. D., G. W. Beebe, and R. W. Miller, "Yellow Fever Vaccination, Avian Leukosis Virus, and Cancer Risk in Man," *Science,* 117:76–77, 1972.

(5) Draper, C. C., "A Yellow Fever Vaccine Free From Avian Leukosis Viruses," *Journal of Hygiene,* (Cambridge), 65:505–513, 1967.

(6) Tauraso, N. M., S. L. Spector, W. G. Jahnes, and A. Shelokov, "Yellow Fever Vaccine: I. Development of a Vaccine Seed Free from Contaminating Avian Leukosis Viruses," *Proceedings of the Society for Experimental Biology and Medicine,* 127:1116–1120, 1968.

(7) Tauraso, N. M., S. L. Spector, R. L. Kirschstein, E. B. Seligmann, Jr., and J. F. Farber, "Yellow Fever Vaccine: II. Antigenicity and Neurovirulence of a Vaccine Seed Free From Avian Leukosis Virus," *Applied Microbiology.*

(8) Tauraso, N. M., S. L. Spector, and R. W. Rimmer, "Yellow Fever Vaccine: III. Antibody Response in Monkeys Inoculated with Vaccine Free From Contaminating Avian Leukosis Viruses," *Archiv fur die Gesamte Virus-forschung,* 37:211–217, 1972.

(9) Fox, J. P., S. L. Kossobudski, and J. Fouseca da Cunlia, "Field Studies on the Immune Response to 17D Yellow Fever Virus. Relation to Virus Substrain Dose and Route of Inoculation," *American Journal of Hygiene,* 38:113–138, 1943.

(10) Tauraso, N. M., R. L. Coultrip, L. J. Legters, A. V. Richman, D. M. Roseberg, T. O. Savadge, A. Shelokov, S. L. Spector, and R. W. Trimmer, "Yellow Fever Vaccine: IV. Reactogenicity and Antibody Response in Volunteers Inoculated with a Vaccine Free From Contaminating Avian Leukosis Viruses," *Proceedings of the Society for Experimental Biology and Medicine,* 139:439–446, 1972.

Review of Rocky Mountain Spotted Fever (RMSF) Vaccine

Rocky Mountain Spotted Fever Vaccine Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* Rocky mountain spotted fever (RMSF) vaccine is prepared by the method of Cox using yolk sacs and chorioallantoic membranes of embryonated eggs infected with *Rickettsia rickettsii.* This material is purified by ether extraction, inactivated with formaldehyde and ethylene oxide, and contains 0.0037 percent formaldehyde, 0.01 percent thimerosal, and up to 0.04 mg/ml of ethylene oxide. The nitrogen content ranges from 4 to 5 mg/ml. The vaccine is tested for potency and safety by the official methods required by the Bureau of Biologics.

a. *Recommended use.* (Quoted from ACIP, see Ref. 1.)

Rocky mountain spotted fever vaccine is not recommended for use in the general population because disease is uncommon and the vaccine is of limited effectiveness. However, it is recommended for laboratory personnel working with *R. rickettsii* and might be considered for persons whose occupations result in exposure to ticks in endemic areas. For persons with only recreational exposure to ticks, protective clothing and deticking should be emphasized.

The Lederle label (revised June 1972) follows the recommendations of ACIP except in emphasis, e.g., "Other persons who may be unduly exposed to possible tick bite because of circumstance of environment such as campers, rangers, etc. in endemic areas should be protected by prophylactic vaccination."

b. *Contraindications.* Listed contraindications and precautions follow reasonable and practical guidelines for the inoculation of biological products. A note regarding effect of prior administration of antibiotics affecting immune response is included for unknown reasons.

2. *Analysis.*—a. *Efficacy.* The literature on the efficacy of RMSF vaccine in the protection of man is sparse and provides little basis for any confidence that the vaccine protects against disease although it may perhaps lower the fatality rate. The most recent report, that of DuPont et al. (Ref. 2) describing a comparative study of the active immunity induced in man by inactivated *R. rickettsii* concludes that killed vaccines, which are regarded as efficacious (based on the results of guinea pig protection tests and uncontrolled vaccine studies) are not effective in preventing RMSF in man. Cox in 1959 (Ref. 3) stated:

Vaccination is an effective method of prophylaxis [and] the vaccines have a definite protective value * * *. The vaccine usually affords complete protection against relatively mild strains, but may be less effective against more virulent ones. Most children are fully protected * * * whereas adults are fully protected only occasionlly.

Although earlier data derived from uncontrolled studies using killed tick-grown vaccine suggested an ameliorating influence, data on the protective capacity of the current egg-grown vaccine are more limited (Ref. 4). It is generally accepted that insofar as guinea pig potency and immunogenicity are concerned, both preparations are comparable (Refs. 2 and 5).

Data to support the induction of a solid immunity in man following vaccination with the Cox-type preparations are lacking. One can state that a number vaccinated adults can still be infected and develop clinical disease even when exposed to low-dose challenge inocula of *R. rickettsii* (Refs. 2 and 6).

The potency test of RMSF vaccine is based on the ability of the vaccine to immunize guinea pigs and to protect them against challenge inoculation, and procedure almost unchanged from 1945. Six or more normal male guinea pigs, weighing approximately 500 grams each, are inoculated subcutaneously with 1 ml of the vaccine under tests.

Ten days after injection, the animals are tested for immunity to a previously determined challenge strain of spotted fever rickettsiae.

The challenge does is injected intraperitoneally and consists of 10 percent infected spleen tissue suspension, or of infected guinea pig blood, or of an appropriate dilution of infected yolk sac suspension. Not less than six normal male guinea pigs are given the same infecting dose of the same material to serve as controls. Both the vaccinated and the conrol animals are observed for 12 days for the effectiveness of the immunization, with body temperatures taken daily during the period.

At least two-thirds of the immunized guinea pigs must not show a temperature elevation above 39.6°C after the third day, nor show overt signs of infection, for the vaccine to be satisfactory. In the control group, at least two-thirds of the animals must show a characteristic temperature curve and other manifestations of infection with the strain of spotted fever rickettsiae used. At least 50 percent should succumb and show the pathological findings characteristics of infection with *R. rickettsii.*

b. *Safety.* The manufacturer's submission noted that for the doses distributed to the general public during 1969 to 1972, there were no complaints. This probably indicated more the failure to report of complaints than inherent safety. The Bureau of Biologics has released nine lots from Lederle in the past 5 years.

c. *Benefit/risk.* The lack of evidence concerning safety plus a similar lack of

evidence for effectiveness suggests an unfavorable benefit/risk ratio.

d. *Labeling.* Labeling should be in accordance with conclusions and recommendations of this review.

3. *Conclusions.*

a. *Critique.* Our assessments are predicated on the above review combined with the following considerations:

Recognition that RMSF is increasing in this country (Fig. 6) and that most cases occur in the Southeastern United States (Fig 7). It is referred to as tick-borne typhus by CDC partly to emphasize this latter point. Most cases in this country occur in children (70 percent), and the overall mortality rate is 5 to 10 percent (Ref. 7).

(2) Recognition that vaccine propylaxis is but one of several measures to control infections and that the vaccine's applicability to the current tick-bone typhus problem in this country is limited to certain occupational and geographical areas (Ref. 8).

(3) The effectivenses of this vaccine in protecting man against RMSF is highly questioned. While a much better vaccine is certainly needed, removal of the present vaccine from the market would make this possibly prophyulactic measure completely unavailable.

b. *Recommendations.*

(1) The Panel recommends that this product be placed in Category IIIA and that the appropriate license be continued on an interim basis pending completion of testing and conformance with recommendations of this report because, while there is no substantial evidence of safety and effectiveness, there is information based on published reports and/or physician surveys which may be deemed to be presumptive evidence of safety and effectiveness for this product. Licensure should be continued for a period of 2 years from the date of issuing of the final order based on this proposal during which time the required substantiating data are to be obtained. Further extension of licensure should depend on the development of convincing evidence for increased potency.

(2) If substantiating data can be obtained, consideration should be given to amending current potency standards (using guidelines similar to those specified in the Armed Forces Epidemiologic Board's recommendations for epidemic typhus vaccine) to provide for a defined whole rickettsial organism content and for the use of a reference preparation in a meaningful assay system.

(3) Mobilization of financial support through the Bureau of Biologics, NIH, and other agencies for research in rickettsial diseases and especially for the development of effective prophylactic measures to replace the current vaccine should be considered.

(4) Safety standards for this vaccine should be updated to provide limits for endotoxin content and for the exclusion of latent viruses, mycoplasma, and other extraneous agents prior to inactivation.

References

(1) "Recommendations of the Public Health Service Advisory Committee on Immunization Practices," in "Immunization Against Diseases," Center for Disease Control, Public Health Service, Department of Health, Education, and Welfare, p. 111, 1972.

(2) DuPont, H. L., R. B. Hornick, A. T. Dawkins, G. G. Heiner, I. B. Fabrikant, C. L. Wisseman, Jr., and T. E. Woodward, "Rocky Mountain Spotted Fever: A Comparative Study of the Active Immunity Induced by Inactivated and Viable Pathogenic Rickettsia rickettsii," *Journal of Infectious Diseases,* 128:340–344, 1973.

(3) Cox, H. R., "The Spotted-Fever Group," *in* "Viral and Rickettsial Infections of Man," 3d Ed., Edited by T. M. Rivers and F. L. Horsfall, Jr., J. B. Lippincott Co., Philadelphia and Montreal, pp. 846–847, 1959.

(4) Parker, R. R., "Rocky Mountain Spotted Fever: Results of Fifteen Years' Prophylactic Vaccination," *American Journal of Tropical Medicine,* 21:369–383, 1941.

(5) Bell, E. J., and H. G. Stoenner, "Spotted Fever Vaccine; Potency Assay by Direct Challenge of Vaccinated Mice with Toxin of Rickettsia Rickettsii," *Journal of Immunology,* 87:737–748, 1961.

(6) Johnson, J. E., III and P. J. Kadull, "Rocky Mountain Spotted Fever Acquired in a Laboratory," *New England Journal of Medicine,* 277:842–847, 1967.

(7) Hattwick, M. A. W., A. H. Peters, M. B. Gregg, and B. Hanson, "Surveillance of Rocky Mountain Spotted Fever," *Journal of the American Medical Association,* 255:1338–1343, 1973.

(8) Smadel, J. E., "Status of the Rickettsioses in the United States," *Annals of Internal Medicine,* 51:421–435, 1959.

Review of Typhus Fever Vaccine

Typhus Fever Vaccine, Inactivated Manufactured by Lederle Laboratories Division, American Cyanamid Co., Eli Lilly & Co., and Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* The Lederle Laboratories typhus fever vaccine is prepared by the method of Cox from chick embryo yolk sacs infected with *Rickettsia prowazekii.* The yolk sac material is purified and inactivated with formaldehyde. The vaccine is diluted in a phosphate buffered solution containing 0.3 molar glycine. Thimerosal (1:10,000) is added as a preservative.

The Eli Lilly & Co. typhus fever vaccine is a suspension of epidemic typhus rickettsias *(Rickettsia prowazekii)* prepared from refined material derived from an aqueous suspension of infected yolk sac membrane. The organisms are inactivated by formaldehyde and suspended in isotonic sodium chloride solution. The vaccine is preserved with thimerosal solution, 1:10,000.

The Merck Sharp & Dohme typhus fever vaccine is described as containing killed *Rickettsia prowazekii* organisms grown on the yolk sac of developing chick embryos, in amounts sufficient to meet standards of potency as specified in 21 CFR 610.10. The diluent is a physiological solution of sodium chloride. The preservative is thimerosal in a final concentration of 1:10,000.

a. *Recommended use.*

(1) *Dosage.*

(i) *Lederle vaccine.* The package insert dated June 1969 recommends, for adults, two subcutaneous injections of 0.5 ml each with an interval between doses of not less than 4 weeks. If this interval is not practical, the second dose may be given prior to embarkation to an endemic area. A booster dose of 0.5 ml should be given at yearly intervals as long as a threat of exposure continues.

For children under 10 years of age, one-half the adult dose is recommended.

(ii) *Merck Sharp & Dohme vaccine.* The Merck Sharp & Dohme vaccine presumably is prepared primarily for the military establishment since the package insert recommends a dosage of one injection of 0.5 ml to be given during basic training, with a reinforcing dose of 0.5 ml to be given to the unit going overseas. Nonmilitary personnel are to receive two injections of 0.5 ml at intervals of not less than 4 weeks. The reimmunization dose is 0.5 cm^3. The package insert is dated February 1963.

(iii) *Eli Lilly & Co. vaccine.* The package insert, dated June 12, 1972, recommends, for adults, a dosage of two subcutaneous injections of 1 ml each with an interval of 4 or more weeks between injections. Booster injections of 1 ml should be administered at intervals of 6 to 12 months for as long as threat of exposure continues. For children the recommended dosage for primary immunization is 0.5 ml on each of the two occasions and the booster injection may be from 0.5 to 1.0 ml according to the individual's age.

Immunization is recommended for such persons as scientific investigators, medical or laboratory personnel, and those whose work brings them into areas where the disease actually occurs, e.g., anthropologists, archeologists, geologists, oil field construction workers, missionaries, etc.

(2) *General comment.* Local reactions showing varying degrees of redness and tenderness, and systemic reactions as evidenced by chilliness, generalized

aching, headache, and fever, may occur in a variable percentage of individuals receiving typhus fever vaccine.

b. *Contraindications.* Immunization should be postponed in the presence of acute infections. The vaccine should not be administered to persons suffering from debilitating diseases and should not be given to individuals receiving immunosuppressant drugs.

Because it is produced from rickettsii grown in chick embryos, the vaccine is contraindicated in persons sensitive to egg proteins.

2. *Analysis.*

a. *Efficacy.*

(1) *Animals.* Protocols on each commercial lot of vaccine must be submitted to the Food and Drug Administration to show that minimum potency and safety requirements have been met. The safety tests involve mice, guinea pigs, and rabbits, and the procedures are essentially those outlined in the review of rocky mountain spotted fever vaccine prepared by Lederle Laboratories.

(2) *Humans.* Vaccine produced according to the minimum requirements established by NIH was utilized by the Armed Forces during World War II. Most of the evidence as to its efficacy therefore came from the military establishment, primarily the Army, and very few additional data have been added.

In 1947, Sadusk (Ref. 1) reported

> * * * in the period January 1, 1942, to December 31, 1945, there were reported in the entire United States Army 64 cases of epidemic typhus, 603 cases of murine typhus and 6,685 cases of tsutsugamushi fever or scrub typhus. There were no deaths during this period from epidemic typhus fever.
>
> While no conclusions can be drawn concerning a reduction in the incidence of epidemic typhus by prophylactic immunization with Cox type ether-extracted typhus vaccine, it appears definite that such vaccination does serve to greatly modify the disease if it occurs in an adequately vaccinated person and does render the deaths from typhus practically nil.

Comments concerning efficacy will be considered further under Critique.

b. *Safety.*

(1) *Animals.* Animal safety tests must satisfy FDA requirements for safety and efficacy.

(2) *Humans.* There is no evidence that the vaccine, when used under normal conditions and in accordance with the precautions given is associated with an unusual incidence of adverse reactions and no fatalities, so far as the Panel is aware, have been reported.

c. *Benefit/risk.* See b. Safety, (2) Humans, above.

d. *Labeling.* This appears to be adequate.

3. *Conclusions.*

a. *Critique.* The most extensive experience with killed typhus fever vaccines has been that of the Department of the Army and it is to this experience that serious consideration was given in evaluating these vaccines. Much of the critique that follows is taken from reports of the Commission on Rickettsial Diseases, Armed Forces Epidemiological Board, and especially that of Dr. Irene B. Fabrikant, presented before the Commission at its annual meeting November 30–December 1, 1972, at the Walter Reed Army Institute for Research, Washington, DC.

Basically the problems are: (1) Although a series of vaccines may pass the minimum requirements, the individual lots may be quite variable in their antigenic composition and potency, and (2) current potency tests are highly unreliable because they are incapable of distinguishing between vaccines of markedly different potency. Because of these variations in antigenic composition and potencies, the antibody response to these vaccines, aside from being unpredictable, has in general been poor.

Studies by the Commission on Rickettsial Diseases have led to a simple procedure for obtaining a direct count of rickettsial bodies contained in a vaccine and this in turn provides an alternative method to complement fixation and animal tests for assaying a vaccine for potency. The development of a simple batch purification technic permits flotation of yolk sac in high density sucrose and provides a means for removing as much as 90 percent of this material from fresh or formalin killed rickettsial preparations. Recovery of rickettsiae, based upon direct counts, is essentially quantitative, and for live rickettsial preparations, there appears to be no loss in the titer of the toxin. It was noted that subcutaneous inoculation of a single dose of such killed rickettsial vaccine preparations into guinea pigs elicited both complement-fixing and toxin-neutalizing antibodies in relatively high titer. The erratic serologic response previously noted in guinea pigs (intraperitoneal inoculation) was in large part obviated.

In sum, therefore, there is now a method for standardizing antigen content on the basis of total rickettsial count and for evaluating immunogenicity by a single-dose guinea pig potency test based on the fact that the serologic response shows a nearly linear relationship between the log of the number of organisms in the dose and the geometric mean titer of toxin neutralizing antibodies.

Recent reports from the Bureau of Biologics (Refs. 2 and 3) describe the production and evaluation of a reference, inactivated epidemic typhus vaccine. Production closely followed procedures recommended by the Commission on Rickettsial Diseases outlined in a previous section. However, laboratory evaluation of potency did not include electron microscope (EM) counts of rickettsiae or tests for development of antibody (complement-fixing and/or toxin-neutralizing) in guinea pigs given a single subcutaneous dose of vaccine as suggested by the Commission. It included, instead, the now discredited two-dose guinea pig potency test and a careful assay of the complement-fixing antigenicity of the vaccine. The former failed to distinguish between vaccine differing by twofold in potency whereas the latter reliably paralleled such potency for vaccine lots representing a parent lot and 3 lots prepared by successive two-fold dilutions of the parent. It also approximately paralleled the immunogenicity of the same lots in clinical trials in man as measured by titer of toxin-neutralizing antibody developed after a single dose of vaccine. Since these trials identified one vaccine lot as acceptable in terms of reactogenicity and as adequately potent (98 percent seroconversion and GMT of 1:32), it would appear that the Bureau of Biologics now has at hand a satisfactory referency vaccine for use in evaluating the potency of future production lots submitted for release.

The clinical trial raised one potentially important question: the apparent narrow range of rickettsial content which is minimally reactogenic but adequately potent. The one acceptable lot was the second in a series of three lots tested which represented successive two-fold dilutions of a parent lot (not tested in man). The first in the series was too reactogenic (5 of 10 recipients experienced significant constitutional symptoms) whereas the third in the series was appreciably less immunogenic (91 percent seroconversion, GMT of 1:16). If the critical range is indeed so narrow (further clinical trials seem indicated to establish this), than it is critically important to be able to evaluate potency for man by a quantitative and reliable laboratory method. While complement fixation (CF) assay of the set of vaccines tested did prove predictive, it is well recognized that rickettsial antigens can be denatured (as by heat) so as to be of greater diminished immunogenicity but without loss of CF reactivity. Thus, laboratory evaluation must include a

test for immunogenicity such as the one-dose guinea pig test suggested by the Commission.

b. *Recommendations.* The Panel recommends that this product be placed in Category IIIA and that appropriate license(s) be continued on an interim basis pending completion of testing and conformance with recommendations of this report because, while there is no substantial evidence of safety and effectiveness, there is information based on published reports and/or physician surveys which may be deemed to be presumptive evidence of safety and effectiveness for this product.

Consideration should be given to the establishment of new criteria for safety and potency. Examination of the revised specifications for potency advanced by the Commission on Ricketsial Diseases of the Armed Forces Epidemiological Board might provide a starting point.

References

(1) Sadusk, J. F., Jr., "Typhus Fever in the United States Army Following Immunization, Incidence, Severity of the Disease, Modification of the Clinical Course and Serologic Diagnosis," *Journal of the American Medical Association,* 133:1192–1199, 1947.

(2) Mason, R. A., E. B. Seligmann, Jr., and R. K. Ginn, "A Reference, Inactivated, Epidemic Typhus Vaccine: Laboratory Evaluation of Candidate Vaccine," *Journal of Biological Standardization,* 4:209–216, 1976.

(3) Mason, R. A., R. P. Wenzel, E. B. Seligmann, Jr. and R. K. Ginn, "A Reference, Inactivated, Epidemic Typhus Vaccine: Clinical Trials in Man," *Journal of Biological Standardization,* 4:217–224, 1976.

Generic Review of Human Immune Serum Globulin and Specific Human and Equine Immune Serum Globulins

Background

The discovery of antibodies by Karl Landsteiner, the association of antimicrobial substances with particular fractions of plasma, and the more recent appreciation of the molecular basis of humoral immunity provide the background for the prophylaxis or modification of infectious disease processes through the use of concentrated antibody preparations. Alcohol fractionation of the globulin proteins by E. J. Cohn's method is an old and well-tested procedure for concentrating antibodies present in human plasma. Application of the method to pools of plasma prepared from the blood of individual donors provides a product that broadly reflects the antibody spectrum of the general population. The use of such human ISG has afforded clearcut benefits in the modification of Type A hepatitis, prophylaxis against measles, and as replacement therapy in dys- or hypogammaglobulinemias.

In recent years, a more potent and effective ISG has been achieved by selection of blood donors with high antibody titers to a specific virus, e.g., varicella, vaccinia, and rabies. Such virus specific globulin products are in limited supply, and hence are restricted to use in specific clinical situations.

1. *Recommendations of the ACIP.* There are no generic recommendations for the use of ISG. However, the section on hepatitis in "Immunization Against Disease," 1972, CDC, contains specific recommendations for ISG use in hepatitis A. Other sections provide comparable recommendations for other virus-specific preparations.

The following are excerpts from "Immunization Against Disease":

a. *Hepatitis A.* Numerous field studies during the past 2 decades have documented the protection against hepatitis-A conferred by ISG administered before exposure or during the incubation period. Its relative effectiveness depends on timing and dose. When administered before, or within 1 to 2 weeks after exposure to hepatitis-A, in the appropriate dose it prevents illness in 80 to 90 percent of those exposed. However, because ISG may not suppress inapparent infection, long-lasting natural immunity may result.

The decision to give ISG is based on assessing the possible hepatitis exposure. If the exposure could have resulted in infection, ISG should be given.

ISG should be given as soon as possible after a known exposure. Its prophylactic value is greatest when given early in the incubation period and decreases with time after exposure. The use of ISG more than 6 weeks after exposure or after onset of clinical illness is not indicated.

Specific recommendations: Household and institutional hepatitis-A case contacts, hepatitis-A needle exposure, common-source hepatitis-A exposure, chimpanzee handlers and travelers to foreign countries.

b. *Measles.* To prevent or modify measles in a susceptible person exposed more than 48 hours before, MIG or standard Immune Serum Globulin (ISG), 0.1 ml/lb, should be given. He should be given live measles vaccine about 3 months later, when the measles antibody will have disappeared, if then at least 12 months old.

c. *Rabies.* Hyperimmune serum has proved effective in preventing rabies. Its use in combination with vaccine is considered the best post-exposure prophylaxis. However, the only preparation of antirabies serum currently available in the United States is of equine origin. Because horse serum has induced serum sickness in at least 20 percent of those who have received it, it should be used only when indicated.

Hyperimmune equine serum is recommended for all bites by animals in which rabies cannot be excluded and for nonbite exposure to animals proven or suspected to be rabid * * *. When indicated, antirabies serum should be used regardless of the interval between exposures and treatment.

However, in 1974 Human Rabies Immune Globulin (HRIG) was licensed, and since 1977 it has been available in adequate supply (Ref. 1). More recent recommendations by ACIP suggest it as a preferred alternate to hyperimmune serum (Ref. 2). The recommended dose of HRIG is 20 IU/kg. Up to 50 percent of the globulin dose should be used for infiltrating the wound and the rest for intramuscular injection.

d. *Vaccinia. Vaccinia Immune Globulin (VIG).* In its recommendations the ACIP considers the use of VIG prophylactically, in such situations as exposure of susceptible persons to smallpox; exposure of eczematous persons to vaccinated household contacts; to minimize complications of vaccination (when absolutely required) in high-risk groups; and therapeutically for any complications of vaccination. These applications are described in detail in the specific product review. Ostensibly the product is no longer being produced in the United States, and hence its future availability is in doubt.

e. *Varicella-Zoster immune globulin (ZIG).* This is a gamma globulin fraction of high antibody titer (1:128 or greater) prepared from plasma obtained from patients convalescing from herpes zoster; it is not a licensed product and may be used only under an Investigational New Drug (IND) (held by CDC). As of 1972, ACIP (Ref. 3) notes that ZIG has been shown effective in preventing varicella when given within 72 hours of exposure and that still under study is its effectiveness: (1) when given later than 72 hours after exposure; (2) for modification of established varicella or zoster; (3) for prevention of dissemination of herpes zoster; and (4) for control and prevention of varicella outbreaks. At the present "ZIG is indicated for the prevention of varicella in susceptible high-risk individuals who have had close V–Z exposure (e.g., household)." Susceptibility can be determined by the Varicella-Zoster (V–Z) fluorescent antibody test. The recommended dose is 5 cc given intramuscularly.

f. *Other products.* There are no current recommendations for passive immunization against mumps, poliomyelitis, or rubella.

2. *Other Indications.* The recommendations cited above cover the specific clinical indications where the use of ISG or specific-immune globulins has been shown to be of benefit. Another and widely accepted indication for ISG is its use as replacement therapy in patients with laboratory documented humoral immune deficiency disease. However, although ISG (and occasionally plasma) therapy is an appropriate therapeutic approach, it is in this area of immunodeficiency that the most common abuses of ISG occur. Diagnoses of recurrent lower respiratory tract "infections"; allergies, including asthma; prematurity; and "failure to thrive" are not adequate indications unless accompanied by specific laboratory evidence of immune globulin deficiency. Similarly, exposure of women to rubella in the first trimester of pregnancy has been cited as an indication; however, use of ISG may modify the maternal illness without protecting the fetus while confusing the serologic status (the use of rebella immune globulin might be considered for exposed individuals where abortion is not permitted).

Probably because of the dilution of antibody which occurs in pools of ISG (derived from at least 1,000 donors), it has not been shown unequivocally to be effective in preventing or modifying hepatitis-B, nor in preventing varicella, although in the latter instance there is some evidence that it may alleviate the disease. With the recognition of hepatitis B surface antigen (HB_sAg), and the ability to assay sera for the corresponding antibody (anti-HB_s), large-scale studies were undertaken to determine the prophylactic effectiveness of both ISG and hepatitis B immune globulin (HBIG). As a result of these studies, HBIG was licensed in 1977.

3. *Comments on PHS Regulations.* Public Health Service regulations deal with processing methods, definitions of lot, final product, and potency, and conclude with some general requirements. On the whole, these rules reflect the technology of the 1960's. More quantitative definitions exist for IgG, the relative content of other immunoglobulins and of contaminating serum proteins. There is no consideration of aggregates, which are the presumed cause of severe reactions and which thus preclude administration of ISG directly into the vascular system. There are no regulations governing specific immune serum globulin other than measles immune globulin, the measles antibody level of which is compared with that of a reference preparation; a two-fold variation in the assay is permissible. It may be noted that, for ISG, a measles antibody level of at least one-half that of the same reference preparation is required.

Analysis

1. *Efficacy*—a. *Hepatitis*—(1) *Hepatitis A.* Although no test for assay of hepatitis A antibody has been available until recently, there is abundant clinical evidence demonstrating the efficacy of ISG in the prevention of Type A hepatitis.

Stokes and Neefe (Ref. 5) and Gellis et al. (Ref. 6) found that ISG could control the severity of viral hepatitis (hepatitis A) epidemics, but had limited value in controlling hepatitis caused by transfusion of whole blood or plasma.

Ashley (Ref. 7) found that the incidence of infectious hepatitis (hepatitis A) in an institution for the mentally retarded was reduced tenfold after use of ISG as a prophylactic measure. The dosage was 0.01 ml/lb of body weight.

Brooks et al. (Ref. 8) and Hsia et al. (Ref. 9) showed the prophylactic effectiveness of ISG in reducing the secondary attack rate in small family groups. Exposed untreated children had a secondary attack rate of 25 percent to 35 percent. Adults in the same category had rates of 0 to 4 percent. Children and adults treated with ISG (0.01 ml/lb) had attack rates of 0 to 2 percent and 0 to 3 percent, respectively.

Stokes (Ref. 10) cites a study in which 40 of 50 persons given 0.06 ml of ISG per pound of body weight were immune 9 months later to experimental infections with hepatitis virus (hepatitis A).

The results of five ISG trials described by Krugman (Ref. 11) further confirmed the efficacy of ISG for the prevention or modification of infectious hepatitis (hepatitis A).

(2) *Hepatitis B.* As noted in an earlier section (Other Indications), both ISG and Hepatitis B Immune Globulin (HBIG) are geing evaluated for prophylactic efficacy against hepatitis B under several exposure circumstances, including "needle-sticks" and work in dialysis units. In the meantime, since the potential benefits from the use of both preparations clearly outweigh known risks, HBIG has been licensed for use in instances of possible exposure to hepatitis B.

b. *Measles.* Well before the development and application of measles vaccines, the efficacy of gamma globulin was recognized both for prevention of the disease (when given in the first 2 days following exposure) and for its modification (when given later, or in lower doses). Dose-dependency of the end result was clear, and with the development and application of the Edmonston live attenuated-virus measles vaccine, it became evident that simultaneous administration of antibody was required to minimize side effects. The original recommendation was that 0.02 ml/kg of measles immune globulin be administered with the vaccine. However, excessive amounts of antibody in the specified volume woud render the vaccine inefficacious. Hence, it became necessary to provide immune globulin with known, predetermined antibody content.

With the development of further attenuated vaccines, the need for concurrent administration of gamma globulin was obviated and with it the need for careful definition of the maximum antibody concentration of measles immune globulins. Thus prevention or modification of measles in exposed susceptible individuals is adequately achieved at present with standard ISG preparations. Their release depends in part on a *minimum* concentration of measles antibodies.

c. *Rabies.* Postexposure immunotherapy (or immunoprophylaxis), until recently had undergone relatively little change since its introduction by Louis Pasteur in the last century. The underlying theoretical basis is that, during the usual relatively long postexposure incubation period, an active immune response of sufficient magnitude to overcome infection and prevent disease can be induced. The efficacy of Pasteurian treatment is frequently questioned, but rigidly controlled field trials in man are not feasible. However, there is little doubt that treatment often prevents fatal rabies; failures occur chiefly in instances of severe exposure with a short incubation period. Observations in India of persons bitten by proved rabid animals have clearly shown the protective effect of immunization when vaccine was available and used (the comparison group consisted of persons for whom treatment was not available).

Antirabies vaccines induce the development of serum neutralizing antibody. This process, however takes time. Antibody rarely appears before 10 days but usually is detectable by 15 days after start of treatment. Assuming that protection is mediated by antibody, it is reasonable to expect that providing pre-formed (passive) antibody as vaccine treatment begins will bridge the gap and increase the level of protection. Working in experimental animals,

Koprowski (Ref. 12) and Habel (Ref. 13) demonstrated that this is indeed true. Koprowski's work emphasized the need to give immune serum (IS) early, i.e., within 72 hours of exposure, and Habel showed the value of local infiltration of IS around the inoculation site to help localize the virus. There is no evidence to suggest that antiserum given later is of benefit, and indeed studies in experimental animals raise the possibility that it may be harmful. A rabid wolf in Iran provided the first opportunity for a semicontrolled study among severely exposed humans. The numbers were small, but use of IS with vaccine appeared highly, although not invariably, protective, even in one patient whose exposure amounted to intracerebral injection of rabies virus (Ref. 14). Examination of sera obtained serially from these patients showed that the use of IS plus NTV resulted in the continuous presence of antibody after treatment had begun (Ref. 15). Subsequent experience, briefly summarized in part by Johnson (Ref. 16), provides further, fairly extensive documentation of the usefulness of IS. An experimental study in guinea pigs related protection to the severity of challenge; vaccine alone conferred good protection against mild challenge, but against severe challenge, IS was needed in addition to the vaccine (Ref. 17).

Few well-controlled animal studies of postexposure immunotherapy have been conducted until recently. In a series of studies using mice and a viral isolate with relatively long incubation period, Baer and Cleary (Ref. 18) found that the virus tended to remain localized (outside the CNS) longer than had been generally appreciated, up to 18 days in some animals. Additionally, they observed that antiserum alone used soon after viral inoculation tended to prolong the incubation period rather than to prevent the disease.

Sikes et al. (Ref. 19), using rhesus monkeys, compared the protective effect of different vaccines given postexposure, and also the protective capacity of antiserum produced in homologous or heterologous animal species. The results were surprisingly unimpressive with respect to the efficacy of serum alone, and a few animals showed the prolonged incubation phenomenon seen in mice.

Recent observations on rabies-related rhabdoviruses in mice are of some interest. In a study of the postexposure effects of immunotherapy in animals infected with Lagos bat virus, Tignor et al. (Ref. 20) found that if administration of passive antibody to immunosuppressed mice was delayed the outcome was rapidly lethal; the same effects were observed with transfer of spleen cells from immunized mice. Such studies, although indirect, may serve to shed light on poorly understood aspects of the pathogenesis of rabies.

In 1960, standards for antirabies serum were established designating an International Standard (equine) antiserum and defining the International Unit (IU) as the activity contained in 1 mg of the International Standard (Ref. 21). The International Standard Antiserum contains 80 IU per ml, and antisera produced for distribution must be shown to be at least as potent as the International Standard (if first comparison shows this, the antiserum passes; if not, two more comparisons are allowed, and if both are satisfactory, the antiserum is approved).

Until recently, the only antisera available in the United States have been preparations of immune globulin of equine origin, which pose the serious problems of serum sickness and anaphylaxis. Various figures for reaction rates are given, but a report of experience in El Paso is illustrative (Ref. 22). Among 526 patients, the overall occurrence of serum sickness was 16.3 percent, ranging with age from 12.3 percent in the 0 to 5 age group to 46.3 percent above age 15. Disturbingly, patients treated from September 1959 to January 1964 had less frequent reaction problems (10 percent of 351) than did those treated between February and September 1964 (29 percent of 175). This may reflect a dosage effect.

An obvious approach to this problem is to employ homologous (human) antiserum. An early study suggested that production of HRIG is feasible, that it is as protective in animals (three species) as that of equine origin, and that, at least in dogs, homologous antiserum is more effective than heterologous antiserum (which would be eliminated more rapidly) (Ref. 23). In clinical trials in man, Cabasso and colleagues (Refs. 24 and 25) reported that the half-life of HRIG is twice that of equine immune globulin and that a dose of 20 IU does not suppress active response to DEV (16 dose course, 14 daily plus an additional dose on days 24 and 34). Rubin et al. (Ref. 26) confirmed the longer persistence of antibody in patients receiving HRIG but emphasized the need to preclude suppression of an active immune response to the vaccine. More recently, Hattwick et al. (Ref. 27) reported that HRIG in doses of 15 or 40 IU interferred with the response to 16 doses of DEV but not to that in a 23 dose course. This last study provides the basis on which recommendations for the use of HRIG were developed. Currently, this product has largely replaced equine rabies immune globulin. A very recent study describes the treatment of 45 persons in Iran, bitten by rabid dogs and wolves, with a new human vaccine produced in diploid cells; the vaccine given in conjunction with HRIG, protected all of the treated, exposed subjects (Ref. 28).

d. *Vaccinia.* See the specific product review.

e. *Varicella-Zoster*—(1) *ISG.* There are no varicella antibody potency standards for ISG. Of the several studies that have been conducted, only that of Ross (Ref. 29) is noteworthy. He studied the course of chickenpox in 773 children in 318 families. ISG in doses of 0.1 ml to 0.6 ml/lb of body weight was administered to 242 children. He concluded that increasing dosage of ISG given within 3 days of exposure produces an increasing diminution of clinical symptoms but no preventive effect was noted.

Rodarte and Williams (Ref. 30) reported that ISG modified and relieved the symptoms in 11 patients suffering from herpes zoster and 5 children with chickenpox.

Trimble (Ref. 31) reported that two interns who received 0.1 ml of ISG per pound of body weight one week before onset of clinical symptoms experienced unusually mild illness. Two other interns with chickenpox did not receive ISG; one died and one had severe symptoms.

Greenberg (Ref. 32) reported that the administration of 5 ml of gamma globulin to 12 of 29 exposed infants did not alter the attack rate.

(2) *Varicella-Zoster Immune Globulin (ZIG).* Evidence for the effectiveness of ZIG is cited in a paper by Judelsohn (Ref. 33).

In 1969 it was shown that ZIG, a gamma globulin fraction of high-titered (1:128 or greater) plasma from convalescing herpes zoster patients, prevented clinical and laboratory evidence of varicella in susceptible children when given within 72 hours of household exposure. Further studies have shown its prophylactic efficacy in high-risk children.

Although ZIG is not a licensed product, the above evidence led Judelsohn (with ACIP assent) to develop the guidelines for the use of ZIG under an IND as stated in section B, ACIP recommendations.

f. *Mumps.* The following is a summary (which includes several papers cited specifically by one manufacturer) of the pertinent literature concerning the efficacy of mumps convalescent serum and mumps immune globulin. The literature falls into two categories: (1)

prevention of mumps in exposed individuals, and (2) treatment of patients with clinical mumps to prevent orchitis.

(1) *Prevention of clinical mumps.* Hess (Ref. 34) administered intramuscularly several ml of whole blood from fresh mumps cases to children exposed to mumps, and reported success in prevention of the disease. This paper, lost for many years and then rediscovered, is not now relevant, however, since the product administered was not gamma globulin and the controls were poorly chosen.

In a trial by Regan, (Ref. 35) convalescent serum obtained from adult patients 10 to 20 days after onset was given, subcutaneously, in 3-ml doses to 81 children in six settings; only 1 child developed mumps. Because susceptibility to infection was based only on history, this study is difficult to evaluate, and its apparently good results are not in accord with subsequent experience.

Zeligs (Ref. 36) used 5 ml intramuscular doses of pooled serum from 6 boys just recovered from mumps; of 44 subjects (susceptibility determined by history) exposed 7 days before treatment none developed clinical mumps.

The report of Lewis and Barenberg (Ref. 37) contains no useful data concerning mumps.

Thalhimer (Ref. 38) gave 20 ml of convalescent serum to children and 40 ml to adults, respectively. The serum was administered by physicians to private patients and their observations were recorded in retrospect. The uncontrolled data do not justify the claim that the treatment prevented mumps nor (in another group) to have reduced the severity of orchitis.

Kutscher (Ref. 39) gave 8 to 10 ml of convalescent serum to 51 "susceptible" and exposed boys. Since only one developed clinical illness, he concluded that the serum was "therefore 98.04 percent protective." Again, the uncertain susceptibility of the subjects coupled with lack of controls does not justify the conclusion.

Reed et al. (Ref. 40) gave mumps immune globulin prophylaxis to 56 exposed seronegative individuals during an epidemic of mumps on St. George Island in the Pribilofs; 46 percent of this group developed clinical mumps within 2 to 25 days, an attack rate similar to that among untreated susceptibles in the same population. Moreover, the incidence of orchitis was the same whether or not gamma globulin was given.

Conclusions. The only test of mumps immune globulin for postexposure prophylaxis, in which laboratory determined preexposure susceptibility was known, gave no evidence of a protective effect.

(2) *Treatment of mumps patients.* DeLavergne and Florentin (Ref. 41) took blood from one case of uncomplicated mumps and one case of mumps orchitis and gave 10, 15, or 20 ml subcutaneously.

Of 107 patients not treated, 25 developed orchitis and 9 meningitis. Of 113 patients treated, 5 developed orchitis and 2 meningitis.

Iversen (Ref. 42) studied military patients to whom pooled serum, obtained from other patients 10 to 20 days post-onset of mumps, was given intramuscularly in 40 ml doses. Of 76 cases treated, 21 (27 percent) developed orchitis. Since about 30 percent of untreated patients also developed orchitis, it was concluded that convalescent serum had no effect.

Bailey and Haerem (Ref. 43) summarized all available data and concluded that the results concerning prevention of orchitis were "uncertain." They observed a group of 734 men, ages 18 to 35 with mumps, and established a rate of 19 to 21 percent orchitis. They treated 183 cases with sera (not pooled) collected from patients 3 weeks after onset of mumps, using 10 or 20 ml doses intramuscularly within the first 3 days of parotitis. They observed orchitis rates of 13 percent with the 10 ml dose, and 22 percent with the 20 ml dose but only 4 percent in patients given serum from donors who had orchitis. They concluded that there was no effect, although the last finding was of interest.

Candel et al. (Ref. 44) did an excellent study of the natural history of mumps and mumps orchitis in young adult males. They studied 105 cases of mumps, of whom 75 were controls and 30 were treated on admission with 100 ml of pooled plasma; no difference was noted in the incidence of orchitis between the two groups.

Gellis et al. (Ref. 45) compared the efficacy of gamma globulin prepared from convalescent donors with that from normal donors (Table 39). These products were given alternately in 20 ml doses intramuscularly to patients admitted within 24 hours onset of parotitis; each treated patient, was matched with an untreated control patient.

They concluded that gamma globulin from patients 1 to 3 months convalescent from mumps was effective but that normal ISG was ineffectual.

Reed et al. (Ref. 40) noted that mumps immune gamma globulin (prepared in the same manner as the present product) had no effect on incidence or severity of orchitis. However, these investigators were referring to cases of mumps which developed despite the preexposure use of mumps immune globulin. It would be surprising if the product, having failed to prevent the primary disease, would prevent complications.

Table 39

Gamma globulin prepared from	Group	Number observed	Incidence of orchitis (percent)
Convalescent serum	Treated	51	7.8
	Controls	51	27.4
Normal serum	Treated	67	20.9
	Controls	67	[illegible]

Conclusions. With one exception (the best designed study, Ref. 45), these studies suggest that convalescent serum or normal gamma globulin exert no obvious effect on the incidence of orchitis. In view of the availability of live attenuated mumps virus vaccine, the need for mumps immune globulin should be small, since the populations that would ordinarily be most at risk (military and institutional) can readily be immunized. With respect to parotitis, however, the Gellis study (Ref. 45) suggests that in postpubertal males early use (within 24 hours) of mumps immune globulin may be of some benefit. If the results of this study can be confirmed using a product, prepared by current techniques, this limited but significant need might justify licensure.

g. *Rubella.* ISG not recommended.

h. *Poliomyelitis.* ISG not recommended.

i. *Immunoglobulin deficiency syndromes.* One investigator concludes from a study of 200 agammaglobulinemic and hypogammaglobulinemic children that a monthly maintenance dose (2 ml to 10 ml depending on weight and age and severity of illness) is indicated. He reports that over a period of 1,057 patient-months prior to ISG therapy, 31 patients were hospitalized; with initiation of ISG therapy, one hospitalization occurred from among these same patients in 723 patient-months.

A British study of 176 patients with hypogammaglobulinemia showed that although the death rate was not reduced in the group in general, the incidence of infections was reduced in children under the age of 10 years (Refs. 46 and 47).

Premature infants with gamma globulin deficiency who were treated with immune serum globulin had a lower incidence of staphylococcal infections than did a similar group of untreated infants (Ref. 48).

In an investigation of hypogammaglobulinemia and its relationship to the allergic diathesis,

Goldfarb and Fudenberg (Ref. 49) studied 26 agammaglobulinemic to hypogammaglobulinemic patients. Six of these were congenitally agammaglobulinemic with serum gamma globulin levels of 6 to 100 mg/100 ml. The remainder was classified as hypogammaglobulinemic with gamma globulin levels of 100 to 400 mg/100 ml. The normal range was listed at 800 to 1,200 mg/100 ml. Most of the patients were treated with an empirically determined dose of 10 ml intramuscularly of pooled gamma globulin (provided by the American Red Cross) once a month. Very young children received the same dose. While gamma globulin treatment did not appear to relieve allergic symptoms, 15 of 16 patients treated for 6 months or more showed a decrease in the number of clinically overt infections.

Gordon and Spencer (Ref. 50) also studied hypogammaglobulinemic children who were allergic and suffered from repeated infections. Sixteen of the 17 patients were from families with histories of allergy. These patients responded well to therapy of 2.0 to 4.0 ml of 16.5 percent gamma globulin solution every 4 weeks. All had an acquired hypogammaglobulinemia (five were females), possessed normal isohemagglutinins, and were able to respond to antigenic stimulation.

Conclusions. The foregoing studies, some of which were not well controlled, are consistent in this indication that use of ISG in gamma globulin deficient patients helps to prevent many clinical infections. In all instances, the subjects studied had been shown by laboratory tests to be deficient in serum gamma globulin.

J. *Allergic conditions—"Infectious Asthma."* Brown et al. (Ref. 51) reported that 23 of 29 asthmatic children treated with ISG responded favorably.

Hilman et al. (Ref. 52) concluded from a controlled study of 50 allergic children that there was no significant difference in the effects of ISG over those of placebo in the management of children with allergy.

Redner and Markow (Ref. 53) found in a study of 40 allergic children that minute doses of ISG of placental origin were effective in the control and prevention of various types of allergic manifestations. Harner and Knerr (Ref. 54) reported inconclusive results from a study of 42 asthamatic children at an Army base. Injection of placental ISG reduced asthmatic episodes by 72 percent from the preceding year. However, saline solution and ISG both were equally effective in diminishing wheezing during or after colds.

Conclusion. The above evidence seems inadequate to support the use of ISG for the treatment of patients with allergies and/or asthma.

2. *Safety.* The administration of ISG is not without some risk. Intravenous administration of the only products currently available in the United States is contraindicated, since it can result in serious systemic reactions. One product (pepsin treated ISG) is licensed for intravenous use, but in some 7 years has never been put on the market, possibly because the half-life of the ISG conferred antibodies in the recipients is very short (mean of 4.5 days, range of 10 hours to 8.5 days), although the titers of specific antibody are claimed not to be affected by the pepsin treatment.

Intramuscular administration of the ISG products available is frequently associated with pain and tenderness at the site of injection, and systemic reactions such as fever, diarrhea, and rashes have been reported. Repeated administration can result in sensitization to heterologous IgG genetic determinants and to thimerosal, a preservative present in all ISG preparations. A variety of allergic manifestations has been reported, the most serious being anaphylactic shock. Although the rate of serious complication is stated in one study (Ref. 4) to be as high as 0.66 percent, most investigators have found that ISG is remarkably nontoxic. Over a 25-year period, some 20 to 25 million doses have been distributed. There are few contraindications.

3. *Benefit/risk.* There is no question that ISG and specific immune serum globulins, although probably over-utilized can be of significant benefit in the prophylaxis and/or attenuation of viral diseases. Generally, it seems most practical to utilize ISG to modify only those diseases not amenable to other methods of specific treatment, e.g., hepatitis A. For passive protection, the use of specific immune serum globulin is to be encouraged, albeit for rather limited distribution. In the following outline, benefit/risk ratios have been considered for specific uses of ISG and certain specific immune serum globulin products.

a. *Hepatitis.* (1) *Hepatitis A.* The benefit of ISG has been clearly established for prophylaxis against hepatitis A, and the risk is negligible; hence, the benefit-risk ratio is highly favorable.

(2) *Hepatitis B.* Recent studies, referred to above, point to a proable prophylatic efficacy of HBIG, and possibly also of ISG. In view of the small risk, the benefit-risk ratio for both products must be viewed as favorable (more so for HBIG).

b. *Measles.* For postexposure prophylaxis against measles, the benefit of both ISG and measles specific immune serum globulins has been well established, and the benefit-risk ratio for these products is highly favorable.

While measles specific immune serum globulin was a safe and desirable adjunct to active immunization with Edmonston B virus vaccines, replacement of these vaccines by more attenuated strains of measles virus makes and the combined administration of specific immune serum globulin and vaccine undesirable for two reasons: (a) an extra inoculation is required, and (b) an active unusual response to the vaccine may be suppressed.

c. *Rabies.* (1) *Equine rabies immune globulin.* For rabies antiserum (equine rabies immune globulin), the benefit-risk ratio, as with rabies vaccine, varies with the likelihood of development of actual rabies. The risk of major reactions to equine immune globulin is so high that its use is warranted only when there only when there is a strong likelihood of rabies supervening after exposure. However, there is considerable reason (both theoretical and experimental) to regard its use in conjunction with vaccine as a more effective regimen than vaccination alone, at least when the golbulin is administered within 24 hours of infection. Thus, if HRIG is not available and the probability of rabies exposure great, the benefit-risk ratio must be considered as favorable.

(2) *Human rabies immune globulin.* The risk attending use of HRIG is, as it is for ISG, negligible. Its use in recommended dosage, coupled with an appropriately prolonged course of vaccine to insure active antibody response, should afford the same benefit as does equine rabies immune globulin. Hence, the benefit/risk ratio is highly favorable.

d. *Vaccinia.* See specific product review for VIG.

e. *Varicella.* Zoster immune globulin is not a licensed product. There is no good evidence that ISG will prevent varicella in exposed susceptible individuals, and it is only suggestive that it may exert a favorable modifying effect on the disease. This possible benefit provides at best a weakly favorable benefit-risk ratio; however, any importance it has is diminished by the fact that modification of disease is important chiefly in the case of high risk persons (for whom the much more effective ZIG is available under an IND).

f. *Mumps.* With no evidence for beneficial effect in either prevention of mumps or of mumps orchitis, the

benefit/risk ratio for use of ISG for these purposes is essentially nil. For mumps immune globulin, see the specific product review.

g. *Rubella.* Although in some cases ISG used prophylactically has been shown to prevent clinical rubella, it cannot be relied upon to prevent infection. Since the most important potential use of ISG in relation to rubella is to prevent rubella infection in exposed pregnant women, the uncertainty of such a result is a major factor in judging the benfit-risk ratio for ISG so used to be unfavorable.

h. *Poliomyelitis.* Prophylactic use of ISG to prevent poliomyelitis has been fully discredited. Hence, for such use, the benefit-risk ratio unfavorable.

i. *Immune globulin deficiencies.* The evidence that continued treatment of patients deficient in gamma globulin with ISG affords relative protection against common infections appears to outweigh the discomfort of the repeated injections and the risk of the rare reactions associated with such use. Hence, for this purpose the benefit-risk ratio is judged to be favorable.

j. *Allergic conditions and "infectious asthma."* With no convincing evidence of efficacy, use of ISG to treat patients with allergies, or who are subject to attacks of "infectious asthma," entails only risk and no benefit and the ratio obviously is adverse.

Critique

The major problem unique to immune serum globulin of nonhuman origin (for example, equine rabies immune globulin) is the frequent induction of serum sickness. To the extent that HRIG is available for the same use, this problem is overcome. Information at this time (September 1976) is that HRIG is fully available. Additional problems are shared by all preparations of fractionated gamma globulin available in the United States. When given intramuscularly (as they should be), they cause pain and persisting local tenderness, the degree increasing with the dose. Also, when given repeatedly, as in the treatment of patients deficient in gamma globulin, sensitization to the common preservative, thimerosal, and even to heterologous IgC genetic determinants may occur. Finally, serious systemic reactions can result if the product, by accident or intent, is administered intravenously. This precludes use of a potentially useful route of administration. As noted previously, the one ISG product licensed for intravenous use has never been marketed in this country.

The beneficial effects of these products depends on the antibodies present (chiefly IgG). Human ISG products are derived from pools of plasma obtained from donors selected for high specific serum antibody titers, either naturally acquired or stimulated (e.g., rabies and mumps) by specific hyperimmunization. Except for measles immune globulin, minimum specfic antibody titers have not been established. ISG is usually produced from large plasma pools (each lot from some 1,000 donors) on the presumption that antibodies to commonly prevalent agents will be present. However, the only assays required are for measles, poliovirus, and diptheria antibodies. To the extent that ISG is used to combat specific viral infections, e.g., hepatitis A and B, rubella, or varicella, knowledge of specific antibody titers for individual lots of ISG would be desirable and could prove valuable in future efforts to evaluate ISG efficacy for such applications as prophylaxis of rubella, varicella, and even hepatitis A.

Recommendations

1. *Product improvement.* The main efforts here should be to determine the necessity for thimerosal as a preservative and, more importantly, to explore further ways to render the gamma globulin product (a) safe for intravenous administration and (b) more stable.

2. *PHS regulations.* These should be expanded to include standards for acceptable composition of each lot in terms of quantity of IgG and relative content of other immune globulins and of adventitious serum proteins. Also, within the limits of applicable technology, lots of ISG should be characterized with respect to important specific antibody titers. At the present time, in view of ACIP recommendations, information concerning antibody levels to measles and hepatitis A is most pertinent. Labeling should include these titers and, with respect to indications for use, should conform to ACIP recommendations. The regulations also should cover ISG, in particular by establishing potency standards which should be reviewed periodically.

3. *Licensure.* The Panel recommends that immune serum globulins licensed for intramuscular use be placed in Category I, and that for ISG, licenses should be continued for specified uses, which currently should include prophylaxis of measles and hepatitis A and the continuing treatment of patients with gamma globulin deficiencies. Usage should be reviewed periodically in conjunction with ACIP which, thus far, has not addressed the full range of possible uses of ISG.

The question of licensure of ISG products for specific viruses is dealt with in the specific product reviews.

Review of Specific Immune Serum Globulin and Specific Human and Equine Immune Serum Globulin Products

Manufacturers who submitted data for currently licensed ISG products are listed below. With one exception, all of these are licensed only for intramuscular use. For these, the preceding generic statements are believed to constitute and adequate review. These ISG products for intramuscular use should all be placed in Category I as safe and effective for approximately indicated purposes.

Abbott Laboratories
Armour Pharmaceutical Co.
Division of Biologic Products, Bureau of Laboratories, Michigan Department of Public Health
Cutter Laboratories, Inc.
Dow Chemical Co.
E. R. Squibb & Sons, Inc.
Lederle Laboratories Division, American Cyanamid Co.
Massachusetts Public Health Biologic Laboratories
Merck Sharp & Dohme, Division of Merck & Co., Inc.
Osterreichisches Institut fur Haemoderivate G.m.b.H.
Parke, Davis & Co.
Travenol Laboratories, Inc., Hyland Division
Wyeth Laboratories, Inc.

Immune Globulin (Human) pepsin-modified "Gammagee-V" produced by Merck Sharp & Dohme, Division of Merck & Co., Inc., and licensed for intravenous use, should be placed in Category IIIA in view of the inadequacy of information concerning its efficacy. The Panel considers that availability of a product of this type is highly desirable and would encourage the manufacturers to develop more extensive data on efficacy.

Immune Serum Globulin (Human) Manufactured by North American Biologicals, Inc.

No data have been provided by the manufacturer for Immune Serum Globulin (Human) for which they were licensed at the time of this review. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIB and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Antirabies Serum Manufactured by Instituto Sieroterapico Vaccinogeno Toscano SCLAVO

1. *Description.* Antirabies serum 'Sclavo' is a sterile aqueous solution of refined and concentrated globulin obtained from the blood of horses immunized against rabies virus.

Preserved with 0.3 percent m-Cresol. Each ml contains 500 units.

The submission described in adequate detail the various phases of production and testing including: production of rabies vaccine to immunize horses (CNS tissue from rabbits infected with CV 12 rabies virus); the regimens for immunizing horses (repeated subcutaneous doses of vaccine until desired neutralizing antibody titer achieved); collection and processing of plasma (ammonium sulfate precipitation of globulin fraction with standard methods of filtration and dialysis); and basic tests for safety and potency in animals.

a. *Recommended use.* For the prevention of hydrophobia in humans the use of antirabies serum in combination with vaccine is considered the best post-exposure prophylaxis. However, because serum of animal may induce serum sickness or acute anaphylactic reactions, it should be used only when indicated.

Antirabies serum is recommended for most exposures classified as severe and for all bites by rabid animals and unprovoked bites by wild carnivores and bats (see chart).

When indicated, antirabies serum should be used regardless of the interval between exposure and treatment.

Of the recommended dose (1,000 units per 40 lb of body weight), "a portion * * * should be used to infiltrate the wound, and the rest administered intramuscularly."

b. *Contraindications.* No contraindication is given as such. Under the heading of "Side Effects/ Precautions" the statement is made that Patients giving a history of allergic symptoms and/or of previous injections of horse serum may be dangerously sensitive and should receive antirabies serum with the utmost caution. Skin and eye tests for sensitivity (both procedures described in detail) are recommended regardless of patient history.

Labeling. In addition to the above material, the labeling and package insert contain a well-presented discussion of sources and types of exposure, the management of biting animals, and the then current ACIP recommendation.

2. *Analysis.* a. *Efficacy.* See generic discussion. Comments made in the generic review concerning the efficacy of equine antirabies sera apply to this product.

b. *Safety.*

(1) *Animal.* This product meets Federal requirements.

(2) *Human.* See generic discussion. Comments made in the generic review concerning the safety of equine antirabies sera apply to this product.

c. *Benefit/risk ratio.* See generic discussion. Comments made in the generic review concerning the benefit/ risk of equine antirabies sera apply to this product.

d. *Labeling.* The label and package insert are reasonable in general, but specific changes should be made. Under "Manufacturer's indications" the statement that serum therapy should be instituted "regardless of the interval between exposure and treatment" is unsubstantiated by any existing data. In view of the lack of data and the inherent serum sickness hazard of this product, the statement is unwarranted and should not appear.

A further fault with the package insert is the failure to cite any contraindications. The statement concerning persons with an allergic history is weak, particularly in view of the present availability of HRIG.

3. *Conclusions.* a. *Critique.* This product has all the limitations of horse serum for use in humans, and as noted in the generic review carries a high risk of serum sickness and other reactions. Its use also complicates the efficacy of rabies vaccine, a point less well discussed in the package insert than might be. Its use is likely to diminish as human rabies immune globulin becomes available; but limited supply of the latter makes it likely that there will be continued need for a supply of equine antiserum for some time to come. Where human rabies immune globulin is not available, the potential benefits of this product, i.e., decreased risk of rabies, clearly outweigh the product's disadvantages.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that licensure be continued at least until adequate availability of preferred human rabies immune globulin is assured. Even when such assurance has been realized for this country (as is now reported to be the case), there presumably will be a need for antirabies serum elsewhere in the world. The package insert should be revised in accordance with the Panel's recommendations.

Antirabies Serum (Equine Origin) Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* Antirabies serum (ARS), a "refined and concentrated" antiserum obtained from hyperimmunized (with fixed rabies virus) horses, contains phenol (0.4 percent) and phenylmercuric borate (1:20,000) as preservatives. Under this heading, the mode of action is described as "delays virus propagation, thus allowing more time for rabies vaccine to induce antibodies."

a. *Recommended use.* ARS is used as an adjunct in postexposure treatment; it should be given as promptly as possible after exposure. Use is indicated in all persons suspected of exposure, *irrespective of interval elapsed since exposure.* Types of possible exposure are described, as is range of incubation periods; emphasis is given to the import of ARS in cases of severe exposure associated usually with short incubation.

b. *Contraindications.* Positive intradermal or conjunctival test for sensitivity is a contraindication unless required as a life-saving measure.

c. *Diagnosis.* A detailed, very good account of diagnosis of rabies in biting animals is provided followed by, *in italics,* the admonition that initiation of treatment should never await results of laboratory diagnostic tests (but when negative, treatment may be terminated).

d. *Treatment.* Detailed instructions following ACIP and WHO recommendations, for management of suspected exposure, including use of ARS are provided. The equine origin of ARS is emphasized as is the necessity for careful history of allergies and a skin test. A procedure for desensitization is outlined for cases when ARS must be given to sensitive individuals. *Precautions* are carefully stated but also, under this heading, the possible occurrence of immediate anaphylactic reactions and of serum sickness is noted.

e. *Processing.* The basic manufacturing process is summarized. Horse blood is drawn into anticoagulant solution, treated, and globulins precipitated by ammonium sulfate. Subsequent steps include neutralization, addition of preservatives, dialysis, reprecipitation, separation in Sharples centrifuge, further clearing, and final concentration. The resulting clear fluid is sterile filtered and ready for quality control.

2. *Analysis.*

a. *Efficacy.* The submission includes abstracts of revelant literature and a

review (discussed in detail in the generic review).

b. *Safety.*

(1) *Animal.* This product meets Federal requirements.

(2) *Human.* For the finished biological product, the manufacturer stated that *no reactions were reported* (in terms of documented case reports) for the years 1969 to 1974 based on distribution of millions of units in that period.

c. *Benefit/risk ratio.* See generic discussion. The hazard of serum sickness necessarily weighs against ARS as the newly licensed HRIG (Human) becomes available.

d. *Labeling.* The label and package insert are reasonable in general but one specific change should be made. Under "Indications" the statement that serum should be administered to all persons suspected of exposure to rabies "irrespective of the interval between exposure and treatment" is unsubstantiated by any existing data. In view of the lack of data and the inherent serum-sickness hazard of this product, the statement is unwarranted and should not appear.

3. *Conclusions.*

a. *Critique.* The submission documents adequate procedures required to insure potency and freedom from undesired contaminants. It also includes abundant reproductions of published papers, many of which deal more with general management of suspected exposure than with ARS in particular.

b. *Recommendation.* The Panel recommends that this product be placed in Cateory I and that licensure be continued at least until adequate availability of preferred HRIG is assured. Even when such assurance has been realized for this country (as is now reported to be the case), there presumably will be a need for ARS elsewhere in the world. The package insert should be revised in accordance with the Panel's recommendations.

Measles Immune Globulin (Human) Manufactured by Lederle Laboratories Division, American Cyanamid Co.

No data have been provided by the manufacturer for Measles Immune Globulin (Human) for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIB and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Measles Immune Globulin (Human) Manufactured by Parke, Davis & Co.

No data have been provided by the manufacturer for Measles Immune Globulin (Human) for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIB and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

Mumps Immune Globulin (Human)-Hyparotin (R) Manufactured by Cutter Laboratories, Inc.

1. *Description.* A solution of gamma globulin prepared from venous blood of humans hyperimmunized with mumps virus vaccine. [Note: package label says "live" but in fact killed mumps virus vaccine is used.] It contains 16.5 percent ± 1.5 percent gamma globulin dissolved in 0.3M glycine and preserved with 1:10,000 thimerosal. * * * Its mumps antibody content is approximately twenty times that of human mumps immune serum * * * [from sera nonreactive for hepatitis associated antigen] * * *. Hyparotin (R) supplies antibodies for the prevention of mumps.

a. *Recommended use.* Hyparotin (R) is indicated in the prophylaxis of mumps * * * should always be given by the intramuscular route and never intravenously * * *. The physician should make sure that his (sic) patient understands that no specific protective or therapeutic end result can be assured in any given case.

There are insufficient data on the relationship between antibody concentration and protective action in mumps to develop a dosage schedule on a firm scientific basis. Although the dosage schedule suggested below has been arrived at empirically, it appears to be effective in some instances in preventing serious sequelae of mumps in older children and adults * * *.

For prophylaxis in children under age 12, 1.5 ml is recommended; for individuals age 12 and older, the dose is 3 to 4.5 ml. For treatment: "Such treatment can be expected to have little or no therapeutic effect * * * it may, if used as heroic doses, prevent complications such as orchitis * * * [at] not less than five times the minimum prophylactic dose and preferably more.

Precautions. Skin tests should not be done. In most human beings the intradermal injection of concentrated gamma globulin cause (sic) a localized area of inflammation which can be misinterpreted as a positive allergic reaction. In actuality, this does not represent an allergy; rather, it is localized tissue irritation of a chemical nature. Misinterpretation of the results of such tests can lead the physician to withhold badly needed human antitoxin from a patient who is not actually allergic to this material. True allergic responses to human gamma globulin given in the prescribed intramuscular manner are extremely rare.

b. *Contraindications.* Individuals known to have an allergic response to gamma globulin.

2. *Analysis.* See generic statement.

a. *Benefit/risk ratio.* The risk associated with the use of gamma globulin intramuscularly is very small. However, since there is no evidence for benefit when used to prevent mumps, the ratio for this purpose must be considered as unfavorable. When used to treat mumps to prevent orchitis, however, some beneficial effect of an analogous product has been reported. If this can be confirmed for this specific product, a favorable ratio would result.

b. *Labeling.* The Advisory Committee on Immunization Practices recommendations do not include the use of mumps immune globulin in any circumstance and therefore cannot be cited. The label is erroneous regarding live vaccine for immunization. The package insert is quoted above.

3. *Conclusions.* a. *Critique.* As discussed in the generic review, the need for mumps immune globulin is limited but significant. The available data, including the excellent study on St. George Island, provide no evidence for its efficacy in prevention of mumps. Most studies directed at treatment of mumps to prevent orchitis employed convalescent serum and yielded negative results. The well-designed study, conducted in 1945, did show a significantly reduced incidence of orchitis, but this required a very large dose (20 ml) of an experimental preparation derived from mumps convalescent serum.

b. *Recommendation.* The Panel recommends that this product be placed in Category II and that the appropriate license be revoked because there are compelling reasons to assume a lack of effectiveness and an unsatisfactory benefit/risk ratio for this product.

Mumps Immune Globulin (Human) Manufactured by Travenol Laboratories, Inc., Hyland Division

1. *Description.* No labels for distribution in final dosage form have been used since 1971. The sole product

is for bulk distribution and is described as follows:

Cohn Fraction II. Derived from plasma found nonreactive for hepatitis associated (Australia) antigen by counterelectrophoresis. For manufacturing use only. For export only. Not sterile. Not tested for potency, sterility, pyrogen or stability. Must be sterilized by filtration within 24 hours after dissovling. Suitability of final preparation for human use is responsibility of final processor.

Contains no stabilizer or preservative.

Protein is at least 95 percent gamma globulin by electrophoresis.

The manufacturer no longer markets the product directly, and thus cites no specific indications or contraindications.

2. *Analysis.* See generic statement.

3. *Conclusions.*

a. *Critique.* The comments pertinent in the generic review remain pertinent here. There is perhaps an issue about export, but in view of the total lack of evidence of efficacy in controlled circumstances it is not compelling. No labeling was provided.

b. *Recommendation.* The Panel recommends that this product be placed in Category II and that appropriate license(s) be revoked because there are compelling reasons (namely, complete lack of information concerning this product) to assume a lack of safety or effectiveness and an unsatisfactory benefit-risk ratio for this product.

Vaccinia Immune Globulin (Human) Manufactured by Travenol Laboratories, Inc., Hyland Division

1. *Description.* The following is the description given on the package insert:

Hyland Vaccinia Immune Globulin (Human) is a 16.5 (±1.5) percent solution of the gamma globulin fraction of the serum of healthy adults who have been recently immunized with vaccinia virus. The solution has been made isotonic and stabilized with 0.3 molar glycine. It contains 0.1 percent sodium chloride and 0.01 percent thimerosal as a preservative. The antibody content, as determined by tissue culture virus neutralization tests, complies with the United States potency requirements for the product and is approximately equal to that of the World Health Organization's International Standard for Anti-Smallpox Serum. Hyland Vaccinia Immune Globulin (Human) is similar to investigational-use preparations which have been available through the American National Red Cross.

A somewhat more detailed list of the ingredients is as follows:

Cohn Fraction II (gamma globulin) from vaccinia immune Source Plasma (Human)	16.5 ±1.5g
Glycine (stabilizer) (0.3 molar)	2.25g.
Sodium chloride (viscosity-reducing agent)	0.1g.
Thimerosal (preservative)	0.01g.
Water for injection	q.s to 100 ml.

Bulk powder, nonsterile, for export is also described in the manufacturer's submission. Instructions include proper directions for sterilization and a waiver of responsiblity for the final product by Hyland.

Potency of the final product is tested as follows:

Suitable dilutions of the reference and the lot under test are mixed with a constant amount of vaccinia virus, added to a human cell tissue culture system, and observed for their ability to reduce plaque formation caused by the virus alone. From the dilutions of reference and lot under test which produce a 50 percent reduction of plaques, the ratio of the respective potencies is calculated.

The test procedure is an adaption of tests described in the published literature. The detailed protocol for the test is on file with the Bureau of Biologics. Review of the protocol indicates that this is an adequate potency test.

a. *Recommended use:* (1) Prevention or modification of smallpox. It should be used in conjunction with smallpox vaccination or revaccination.

(2) Prevention or modification of the complications of smallpox vaccinations. VIG may be used prophylactically in vaccination, when necessary, of eczematous children or adults, individuals with virus, individuals with other extensive skin lesions, pregnant women, and those at particular risk of encephalitis.

(3) Prophylaxis in vaccination contacts with eczema or other extensive skin disease, immune deficiency diseases, etc.

(4) Treatment of complications of smallpox vaccination, eczema vaccination, vaccinia necrosum generalized vaccinia, accidental infections of the eye, mouth, etc., and vaccinia infection of burns, impetigo, etc.

Recommended dosage is 0.3 ml/kg for prophylaxis and 0.6 ml/kg or more for treatment. Route is intramuscularly, with warnings against intravenous use.

The recommendations of ACIP are not sufficiently detailed for a package insert, and are as follows:

Prophylactic use. Dose. 0.3 ml/kg by the intramuscular route.

Therapeutic use. Dose and indications. 0.6 ml/kg by the intramuscular route. For eczema vaccinatum, progressive vaccinia, or autoinoculation vaccinia of the eye, VIG may be effective. For severe cases of generalized vaccinia, VIG may be helpful in treatment; but such cases almost invariably have a favorable outcome anyway, provided the primary vaccination site heals. For mild cases of generalized vaccinia or autoinoculation not involving the eye, VIG is generally considered unnecessary. For post vaccinial encephalitis, VIG is of no proved therapeutic value.

b. *Contraindications.* Administration of VIG in the presence of active keratitis has resulted in increased scarring in rabbits. Since it is presumed that a similar response might occur in humans, VIG should not be used in the treatment of keratitis caused by vaccinia virus.

2. *Analysis.*

a. *Efficacy.* (1) *Animal.* None available.

(2) *Human.* Most of the published studies of the value of VIG have used products produced by manufacturers other than Hyland. Nevertheless, it is important to review these since they probably would apply equally well to the material under consideration.

(i) *Prophylaxis of smallpox.* The evidence that VIG is effective, in conjunction with vaccination, in preventing smallpox is good but stems from only a few studies. In one study (Ref. 55) of 75 control (vaccination alone) contacts of smallpox cases, 8 developed smallpox and 3 died. Of 56 VIG (vaccination plus vaccinia immune globulin) contacts, 2 developed smallpox and 1 died. In a larger study (Ref. 56) the figures were as follows: of 379 control contacts (vaccination alone) 21 developed smallpox within 14 days; of 326 VIG treated contacts (VIG plus vaccination), 5 developed smallpox within 14 days. The two groups in this study were well matched in every important respect. The calculated combined reduction of smallpox cases achieved by the addition of VIG to prophylaxis was 70 percent.

One other published study (Ref. 57) provided anecdotal data on the mild illness in two individuals given VIG and vaccine several days after exposure.

(ii) *Prophylaxis of the complications of smallpox vaccination.* Evidence for a prophylactic effect in the prevention of eczema vaccinatum is less clear-cut but is provisionally accepted. This complication occurs infrequently after deliberate vaccination of eczematous individuals, even when prophylaxis is not administered. Kempe estimates that only 1 out of 200 vaccinated eczematous children gets eczema vaccinatum. In the report of Sharp and Fletcher (Ref. 58), one case of mild eczema vaccinatum developed among 290 eczematous persons given VIG prophylactically. Another failure of prophylactic VIG is reported by Sussman and Grossman (Ref. 59). Nevertheless, there is a general impression that such prophylaxis is effective (Ref. 60).

There is no evidence that VIG prevents the complications of smallpox vaccination in immune deficiency states, immunosuppression, pregnancy, or skin diseases other than eczema. It is nevertheless recommended in situations where vaccination is imperative.

Prophylaxis in the prevention of encephalitis is illustrated best in the report of Nanning (Ref. 61). Antivaccinia gamma globulin (AGG) was administered in a dose of 2 ml to 53,630 Dutch recruits, aged 19 to 22, and a placebo was given to 53,044. Dutch recruits are thought to have an incidence of encephalitis of 1 in 4,000 primary vaccinations and 1 in 50,000 revaccinations. There were 13 cases of postvaccinial encephalitis in the controls and 3 in the prophylactically treated group. This difference was highly significant ($p < 0.001$).

(iii) *Treatment of the complications of vaccination.* The value of VIG in treatment of eczema vaccinatum must be inferred from uncontrolled reports by Kempe (Ref. 62), Sussman and Grossman (Ref. 59), and Sharp and Fletcher (Ref. 58). The mortality of eczema vaccinatum in children under 2 cared for with supportive therapy alone is quoted by Kempe as 30 to 40 percent. In his group given therapeutic VIG, the mortality was 7 percent (9 of 132). In Sussman and Grossman's group, mortality was 1 of 37, and in Sharp and Fletcher's cases, 2 of 47 died. In the last two reports, methisazone was occasionally used in conjuction with VIG in very ill cases. The overall mortality in these reports, then, is 11 of 216, or 5 percent. All three reports are quite emphatic about the temporal relationship between VIG treatment and clinical improvement in almost all cases.

Treatment of vaccinia necrosum is likewise uncontrolled. Some patients appear to respond and others clearly do not (Ref. 62). Again, its use is recommended.

Treatment of less severe complications of vaccination may also be effective. In the instance of generalized vaccinia, the evidence for efficacy is slim indeed, particularly since this diagnosis is often wrong because the rash is confused with various forms of allergic rash in response to vaccination. Patients with accidental inoculation in crucial areas such as the eye, finger, mouth, etc., appear to respond to VIG, but there are no well-controlled data.

b. *Safety.* (1) *Animal.* The product meets the standards of the "General Safety" tests specified in § 610.11 (21 CFR 610.11). Likewise it has passed sterility tests and tests for pyrogenicity in animals.

(2) *Human.* The data for this particular product are not available. However, there is no reason to believe that the human safety differs from that of other immune serum globulins produced by the same manufacturer.

c. *Labeling.* All labeling should conform to FDA's proposed regulations for labeling for prescription drugs used in man as reported in the **Federal Register** of April 7, 1975 (40 FR 15392) and to the updated recommendations of ACIP.

3. *Conclusions.* a. *Critique.* Vaccinia immune globulin as prepared by Hyland appears to be a useful product as long as smallpox continues to be present somewhere in the world. The evidence for efficacy is at times spotty, but the benefit/risk ratio remains high.

b. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. The Panel has been informed that this product is no longer being produced and expresses the hope that this decision be reconsidered since there is a clear, albeit infrequent need.

References

(1) "Morbidity and Mortality Weekly Report," Volume 24, p. 99, 1975.

(2) "Morbidity and Mortality Weekly Report," Volume 24, p. 29, 1974.

(3) Recommendations of the Public Health Service Advisory Committee on Immunization Practices, "Immunization Against Disease," Center for Disease Control, Public Health Service, Department of Health, Education, and Welfare, p. 68, 1972.

(4) Janeway, C. A., "Use of Concentrated Human Serum Gamma Globulin in Prevention and Attenuation of Measles," *Bulletin of the New York Academy of Medicine,* 21:202–222, 1945.

(5) Stokes, J. and J. R. Neefe, "Prevention and Attenuation of Infectious Hepatitis by Gamma Globulin; Preliminary Note," *Journal of the American Medical Association,* 127:144–145, 1945.

(6) Gellis, S. S. et al., "Use of Human Immune Serum Globulin (Gamma Globulin) in Infectious (Epidemic) Hepatitis in Mediterranean Theater of Operations," *Journal of the American Medical Association,* 128:1062–1063, 1158–1159, 1945.

(7) Ashley, A., "Use of Gamma Globulin for Control of Infectious Hepatitis in Institution for Mentally Retarded," *New England Journal of Medicine,* 252:88–91, 1955.

(8) Brooks, B. F. et al., "Family Outbreaks of Infectious Hepatitis; Prophylactic Use of Gamma Globulin," *New England Journal of Medicine,* 249:58–61, 1953.

(9) Hsia, D. et al., "Gamma Globulin in Prevention of Infectious Hepatitis: Studies on Uses of Small Doses in Family Outbreaks," *New England Journal of Medicine,* 250:417–419, 1954.

(10) Stokes, J., "Passive-Active Immunization in Certain Viral Diseases that Produce Permanent Immunity (Kenneth D. Blackfan Memorial Lecture)," *New England Journal of Medicine,* 255:943–949, 1956.

(11) Krugman, S. et al., "Gamma Globulin Prophylaxis," *Bulletin of the New York Academy of Medicine,* 45:181–188, 1969.

(12) Koprowski, H. et al., "Use of Hyperimmune Antirabies Serum Concentrates in Experimental Rabies," *The American Journal of Medicine,* 8:412–420, 1950.

(13) Habel, K., "Antiserum in Prophylaxis of Rabies," *Bulletin of the World Health Organization,* 10:781–788, 1954.

(14) Baltazard, M. et al., "Essai Practique du serum Antirabique Chez les Mordus par Loups Enragés," *Bulletin of the World Health Organization,* 13:747–772, 1955.

(15) Habel, K. and H. Kobrowski, "Laboratory Data Supporting Clinical Trial of Antirabies Serum in Persons Bitten by Rabid Wolf," *Bulletin of the World Health Organization,* 13:773–779, 1955.

(16) Johnson, H. M., "Viral and Rickettsial Infections of Man," 1965.

(17) Veerarghavan, N. et al., "Value of Antirabies Vaccine with and without Serum against Severe Challenges," *Bulletin of the World Health Organization,* 22:381–391, 1960.

(18) Baer, G. M. et al., "A Model in Mice for the Pathogenesis and Treatment of Rabies," *Journal of Infectious Diseases,* 125:520–527, 1972.

(19) Sikes, R. K. et al., "Effective Protection of Monkeys against Death from Street Virus by Post-Exposure Administration of Tissue-Culture Rabies Vaccine," *Bulletin of the World Health Organization,* 45:1–11, 1971.

(20) Tignor, G. H. et al., "Immunopathologic Aspects of Infection with Lagos Bat Virus of the Rabies Serogroup," *Journal of Immunology* 112:260–265, 1974.

(21) World Health Organization Technical Report, No. 201, 1960.

(22) Karliner, J. S. and G. S. Belaval, "Incidence of Reactions Following Administration of Antirabies Serum; Study of 526 Cases," *Journal of the American Medical Association,* 193:359–362, 1965.

(23) Winkler, W. G. et al., "Evaluation of Human Rabies Immune Globulin and Homologous and Heterologous Antibody, *Journal of Immunology,* 102:1314–1321, 1969.

(24) Cabosso, V. J. et al., "Rabies Immune Globulin of Human Origin: Preparation and Dosage Determination in Nonexposed Volunteer Subjects," *Bulletin of the World Health Organization,* 45:303–315, 1971.

(25) Loofbourow, J. C. and V. J. Cabasso, et al., "Rabies Immune Globulin (Human). Clinical Trials and Dose Determination," *Journal of the American Medical Association,* 217:1825–1831, 1971.

(26) Rubin, R. H. et al., "Human Rabies Immune Globulin. Clinical Trials and Effects on Serum Anti-Globulins," *Journal of the American Medical Association,* 224:871–874, 1973.

(27) Hattwick, M. A. et al., "Postexposure Rabies Prophylaxis with Human Rabies Immune Globulin," *Journal of the American Medical Association,* 227:407–410, 1974.

(28) Bahmanyar, M. et al., "Successful Protection of Humans Exposed to Rabies

Infection. Postexposure Treatment with the New Human Diploid Cell Rabies Vaccine and Antirabies Serum," *Journal of the American Medical Association,* 236(24):2751–2754, 1976.

(29) Ross, A. H., "Modification of Chicken Pox in Family Contacts by Administration of Gamma Globulin," *New England Journal of Medicine,* 267:369–376, 1962.

(30) Rodarte, J. G. and B. H. Williams, "Treatment of Herpes Zoster and Chickenpox with Immune Globulin," *Archives of Dermatology,* 73:553–555, 1956.

(31) Trimble, G. X., "Attenuation of Chickenpox with Gamma Globulin," *Canadian Medical Association Journal,* 77:697–699, 1957.

(32) Greenberg, M., "Gamma Globulin in Pediatrics," *The Medical Clinics of North America,* 31:602–608, 1947.

(33) Judelsohn, R. G., "Immunization against Disease—1972," Center for Disease Control, pp. 67–68, 1972.

(34) Hess, A. F., "A Protective Therapy for Mumps," *American Journal of Diseases of Children,* 10:99–103, 1915.

(35) Regan, J. C., "Serum Prophylaxis of Epidemic Parotitis," *Journal of the American Medical Association,* pp. 279–280, 1925.

(36) Zeligs, M., "Convalescent Serum in Prevention of Mumps," *Journal of Pediatrics,* 1:727–728, 1932.

(37) Lewis, J. M. and L. H. Barenberg, "Use of Convalescent Serum in Treatment of Measles, Chicken Pox, Mumps and Whooping Cough, Including the Prophylactic Value of Parenteral Blood," *New York State Journal of Medicine,* 33:97–99, 1933.

(38) Thalhimer, W., "The Prophylactic and Therapeutic Use of Convalescent Serums: Scarlet Fever, Mumps, and Chicken Pox," *Journal of Pediatrics,* 14:257–261, 1939.

(39) Kutscher, G. W., Jr., "The Use of Convalescent Mumps Serum," *Journal of Pediatrics,* 16:166–170, 1940.

(40) Reed, D., et al., "A Mumps Epidemic on St. George Island, Alaska," *Journal of the American Medical Association,* 199:113–117, 1967.

(41) DeLavergne, V. and P. Forentin, "Prevention of Mumps Orchitis with Injection of Convalescent Serum," *Bulletin of the Academy of Medicine,* 93:362–364, 1925.

(42) Iversen, P., "Complications of Epidemic Parotitis and Experimental Treatment with Convalescent Serum," *Ugeskrift fur Laeger,* 92:167–169, 1930.

(43) Bailey, W. H. and A. T. Haerem, "Some Observations on Efficacy of Convalescent Mumps Serum," *Military Surgeon,* 90:134–139, 1942.

(44) Candel, S., et al., "Mumps Orchitis, with Discussion of Plasma Prophylaxis," *U.S. Navy Medical Bulletin,* 45:97–107, 1945.

(45) Gellis, S. S., et al., "Study on Prevention of Mumps Orchitis by Gamma Globulin," *American Journal of Medical Sciences,* 210:661–664, 1945.

(46) Healy, M. J., "Hypogammaglobulinaemia in the United Kingdom," *Medical Research Council Spec. Rep. Ser. (London),* 310:115–123, 1971.

(47) Hill and Mollison, "Hypogammaglobulinaemia in the United Kingdom," *Medical Research Council Spec. Rep. Ser. (London),* 310:4–8, 9–34, 124–127, 129–310, 1971.

(48) Mathesius, V. J. and V. Maly, "Immunization Trials against Staphylococcal Infections in Premature Infants. I. Passive Immunization Experiments with Normal Gamma-Globulin," *Annals Paediatrici,* 190(4):193–207, 1958.

(49) Goldfarb, A. A. and H. Fudenbert, "Hypogammaglobulinemia and Its Relationship to the Allergic Diathesis," *New York Journal of Medicine,* 61:2721–2731, 1961.

(50) Gordon, B. D. and S. Spencer, "Hypogammaglobulinemia, Common Variant in Children Responsive to Therapy," *Journal of the American Medical Association,* 174:269–272, 1960.

(51) Brown, E. B. and A. Botstein, "The Effect of Gamma Globulin in Asthmatic Children," *New York Journal of Medicine,* 60:2539–2545, 1960.

(52) Hilman, B. C. et al., "Intracutaneous Immune Serum Globulin Therapy in Allergic Children," *Journal of the American Medical Association,* 207(5):902–906, 1969.

(53) Redner, B. and H. Morkow, "Effects of Minute Doses of Gamma Globulin in Children with Active Allergic Manifestations," *Journal of the American Medical Association,* 185:692–695, 1963.

(54) Harner, R. H. and R. J. Knerr, "Gamma Globulin and Its Effect on Infection-Precipitated Asthmatic Episodes in Children," *Annals of Allergy,* 22:438–443, 1964.

(55) Kempe, C. H. et al., "Hyperimmune Vaccinal Gamma Globulin; Source, Evaluation, and Use in Prophylaxis and Therapy," *Pediatrics,* 18:177, 1956.

(56) Kempe, C. H. et al., "The Use of Vaccinia Hyperimmune Gamma-Globulin in the Prophylaxis of Smallpox," *Bullentin of the World Health Organization,* 25:41–48, 1961.

(57) Pierce, E. R. et al., "Antivaccinial Gamma-Globulin in Smallpox Prophylaxis," *Lancet,* 2:635–638, 1958.

(58) Sharp, J. C. and W. B. Fletcher, "Experience of Anti-Vaccinia Immunoglobulin in the United Kingdom," *Lancet,* 1:656–659, 1973.

(59) Sussman, S. and M. Grossman, "Complications of Smallpox Vaccination. Effects of Vaccinia Immune Globulin Therapy," *Journal of Pediatrics,* 67:1168–1173, 1965.

(60) Morbidity and Mortality Weekly Report, Vol. 21, No. 25, Supplement 25–28, 1972.

(61) Nanning, W., "Prophylactic Effect of Antivaccinia Gamma-Globulin against Post-Vaccinal Encephalitis," *Bulletin of the World Health Organization,* 27:317–324, 1962.

(62) Kempe, C. H., "Studies on Smallpox and Complications of Smallpox Vaccination," *Journal of Pediatrics,* 26:176–189, 1960.

FDA Response to the Panel's Recommendations

The FDA is responding to the Panel's recommendations as follows:

1. The Panel recommended that Viral and Rickettsial Vaccines be grouped into regulatory categories as follows:

a. *Category I. Biological products determined to be safe and effective and not misbranded: [and may continue in interstate commerce]* Poliomyelitis Vaccine (Purified), Connaught Laboratories, Ltd., License No. 73; Poliovirus Vaccine, Live, Oral, Trivalent (Orimune), Poliovirus Vaccines, Live, Oral, Type 1, Type 2, and Type 3, (Monovalent) (Orimune), Lederle Laboratories Division, American Cyanamid Co., License No. 17, Poliovirus Vaccine, Live, Oral, Trivalent (Diplovax), Pfizer Ltd., License No. 338; Smallpox Vaccine (in three formulations: Glycerinated Vaccine; Dried Vaccine; Dried Vaccine for Jet Injection), Connaught Laboratories, Ltd., License No. 73; Smallpox Vaccine, Avianized, Lederle Laboratories Division, American Cyanamid Co., License No. 17; Smallpox Vaccine and Smallpox Vaccine Freeze-Dried, Merrell-National Laboratories, Division of Richardson-Merrell Inc., License No. 101; Smallpox Vaccine, Bureau of Laboratories, Michigan Department of Public Health, License No. 99; Smallpox Vaccine (Dryvax), Wyeth Laboratories, Inc., License No. 3; Measles Virus Vaccine, Live, Attenuated (Schwarz Strain), (Lirugen), Dow Chemical Company, License No. 110; Measles Virus Vaccine, Live, Attenuated (M-Vac), Lederle Laboratories Division, American Cyanamid Co., License No. 17; Measles Virus Vaccine, Live, Attentuated, (Attenuvax); Mumps Virus Vaccine, Live (Mumpsvax); Rubella Virus Vaccine, Live (Meruvax); Measles, Mumps, and Rubella Virus Vaccine, Live, M–M–R); Measles and Rubella Virus Vaccine, Live (M–R–Vax); Measles-Smallpox Vaccine, Live (Attenuvax-Smallpox); Rubella and Mumps Virus Vaccine, Live (Biavax), Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Rubella Virus Vaccine, Live (Cendehill Strain) (Cendevax), Recherche et Industrie Therapeutiques, S.A., License No. 430; Influenza Virus Vaccine, Bivalent (Flu-Immune), Lederle Laboratories Division, American Cyanimid Co., License No. 17; Influenza Virus Vaccine, Bivalent (Zonomune), Eli Lilly and Company, License No. 56; Influenza Virus Vaccine, Bivalent (Fluax), Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Influenza Virus Vaccine, Bivalent (Fluzone), Merrell-National Laboratories, Division of Richardson-Merrell Inc., License No. 101; Influenza Virus Vaccine, Bivalent (Fluegen), Parke, Davis and Co., License No. 1; Influenza Virus Vaccine, Bivalent (Chromatograph and Filter Purified Subvirion Antigen), Wyeth Laboratories, Inc., License No. 3; Rabies Vaccine, (Duck Embryo) Dried Killed Virus, Eli Lilly and Company, License No. 56; Yellow Fever Vaccine, Merrell-National

Laboratories, Division of Richardson-Merrell Inc., License No. 101; Immune Serum Globulin, Abbott Laboratories, License No. 43; Armour Pharmaceutical Company, License No. 149; Bureau of Laboratories, Michigan Department of Public Health, License No. 99; Cutter Laboratories, Inc., License No. 8; Dow Chemical Company, License No. 110; E. R. Squibb & Sons, Inc., License No. 52; Lederle Laboratories Division, American Cyanamid Co., License No. 17; Massachusetts Public Health Biologic Laboratories, License No. 64; Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Osterreichisches Institut for Haemoderivate G.m.b.H., License No. 258; Parke, Davis and Co., License No. 1; Travenol Laboratories, Inc., Hyland Division, License No. 140; Wyeth Laboratories, Inc., License No. 3; Vaccinia Immune Globulin (Human), Travenol Laboratories, Inc., Hyland Division, License No. 140; Antirabies Serum, Instituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238; Antirabies Serum (Equine Origin), Lederle Laboratories Division, American Cyanamid Co., License No. 17.

The FDA agrees with the Panel's findings and recommendations and hereby proposes to adopt its conclusions, including proposed labeling revisions concerning product use. Comments and/or additional data on this classification are invited. The following licenses for products in Category I were revoked at each manufacturer's request:

Product	License No.	Manufacturer	Date of revocation
Poliovirus Vaccine, Live, Oral, Trivalent.	338	Pfizer Ltd.	6/12/79
Smallpox Vaccine	101	Merrell-National Laboratories, Division of Richardson-Merrell Inc..	1/3/78
Smallpox Vaccine (Avianized).	17	Lederle Laboratories Division, American Cyanamid Co..	5/24/78
Measles Virus Vaccine, Live, Attenuated (Schwarz Strain), (Lirugen).	110	Dow Chemical Co..	6/21/78
Influenza Virus Vaccine, Bivalent (Zonomune).	56	Eli Lilly and Company.	7/11/77
Influenza Virus Vaccine.	101	Merrell-National Laboratories, Division of Richardson-Merrell Inc..	1/3/78
Yellow Fever Vaccine.	101	Merrell-National Laboratories, Division of Richardson-Merrell Inc..	1/3/78
Immune Serum Globulin.	110	Dow Chemical Company.	6/7/77
Immune Serum Globulin.	258	Osterreichisches Institut fur Haemoderivate G.m.b.H..	7/22/76
Immune Serum Globulin.	43	Abbott Laboratories.	8/15/78

Merrell-National Laboratories, Division of Richardson-Merrell Inc., transferred its manufacturing processes and facilities for manufacturing Smallpox Vaccine, Influenza Virus Vaccine, and Yellow Fever Vaccine, License No. 101, to Connaught Laboratories, Inc. Connaught was issued License No. 711 of January 3, 1978.

Abbott Laboratories transferred its manufacturing processes and facilities for manufacturing Immune Serum Globulin, License No. 43, to Alpha Therapeutic Corp. Alpha Therapeutic Corp. was issued License No. 744 on August 15, 1978.

b. *Category II. Biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce:* Mumps Immune Globulin (Human)—(Hyparotin), Cutter Laboratories, Inc., License No. 8; Mumps Immune Globulin (Human), Travenol Laboratories, Inc., Hyland Division, License No. 140; Mumps Virus Vaccine (Inactivated), Eli Lilly and Company, License No. 56; Mumps Vaccine (Killed), Lederle Laboratories Division, American Cyanamid Co., License No. 17; Adenovirus Vaccine, Parke, Davis and Co., License No. 1; Adenovirus and Influenza Virus Vaccine, Combined, Parke, Davis and Co., License No. 1.

The FDA agrees with the Panel's findings and recommendations concerning these drugs and, in accordance with §§ 601.5 and 601.25(f)(2), FDA intends to publish a notice of an opportunity for a hearing (NOH) to revoke the licenses for these products. Interested persons may comment and/or submit additional data in response to the notice. These revocation proceedings will not be necessary for (1) Mumps Virus Vaccine (Inactivated), the license for which was revoked on April 7, 1977, at the request of Eli Lilly and Company and (2) Mumps Vaccine (Killed), the license for which was revoked on May 24, 1978, at the request of Lederle Laboratories Division, American Cyanamid Company.

Following the publication of standards for inactivated Adenovirus Vaccine in 1957 (see **Federal Register** of September 24, 1957 (22 FR 7560)) several manufacturers were issued product licenses. In addition, two manufacturers received product licenses for Adenovirus and Influenza Virus Vaccine, Combined, Aluminum Phosphate Adsorbed, which is a combination of the Adenovirus Vaccine with another licensed biological product.

During the years subsequent to the issuance of these licenses, it became evident that there were certain persistent problems concerning the contamination of adenovirus with a newly discovered simian virus known as SV40. As a result, licensed manufacturers of these products were advised in October 1964 that no further lots of the inactivated Adenovirus Vaccine could be released until these problems were resolved.

Since 1964, there has been no evidence that these problems have been resolved. In the **Federal Register** of January 3, 1973 (38 FR 48), FDA announced its conclusion that (1) the vaccine cannot be manufactured in a manner that assures its safety, purity, and potency, (2) the additional standards for Adenovirus Vaccine (21 CFR 273.1040 through 273.1045, redesignated as 21 CFR 630.20 through 630.25) should be deleted from the biologics regulations, and (3) the licenses governing any adenovirus vaccines, either singly or in combination, should be revoked. That **Federal Register** announcement also provided a notice of opportunity for a hearing (NOH) to manufacturers of adenovirus vaccines on the Commissioner's intent to revoke all licenses remaining in effect. All manufacturers, except Parke, Davis and Co., requested that their product licenses be revoked. Parke Davis did not respond to the notice. Although no adenovirus vaccine has been released for sale since August of 1964, the Parke Davis product license for these vaccines has not been officially revoked.

The Panel reviewed (as part of their review of pre-1972 licensed products) information on file with the Bureau of Biologics and other information submitted directly to the Panel, including presentations by representatives of Parke, Davis and Co. in April 1974, in support of adenovirus vaccines. The Panel found this information to be inadequate to support the continued licensing and placed

adenovirus vaccines in Category II. Consistent with the procedures established for such products, a NOH covering the Parke Davis vaccines will be published as part of the implementation of the Panel's report. In addition to the lack of proven safety and effectiveness, the agency intends to base revocation, as authorized by § 601.5(b)(2), upon the fact that manufacture has discontinued to such an extent that a meaningful inspection cannot be made. Should the Parke Davis product license for adenovirus vaccines be revoked, a final order also will be published revoking the additional standards for Adenovirus Vaccine.

c. *Category IIIA. Biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in interstate commerce pending completion of testing:* Rocky Mountain Spotted Fever Vaccine (RMSF), Lederle Laboratories Division, American Cyanamid Co., License No. 17; Typhus Vaccine, Lederle Laboratories Division, American Cyanamid Co., License No. 17; Eli Lilly and Company, License No. 56; Merck Sharp & Dohme, Division of Merck & CO., Inc., License No. 2; Immune Globulin (Human), Pepsin Modified, (Gammagee-V), Merck Sharp & Dohme, Division of Merck & CO., Inc., License No. 2.

The FDA agrees with the Panel's findings and recommendations concerning these drugs and, in accordance with § 601.25(f)(3), hereby proposes that products listed in Category IIIA remain on the market and their licenses remain in effect, on an interim basis, pending completion of testing and the submission of acceptable data based on scientifically sound studies (as recommended in the Panel report) to demonstrate efficacy in humans. Such studies shall be in accordance with the Panel's recommendations and § 601.25(h), and shall be completed within 2 years of publication of the final order. Failure to submit adequate data, in the form of a license amendment, within the specified time will result in the publication of a notice of intent to revoke the product license. Comments and/or additional data on this classification are invited.

The additional studies will not be necessary for Rocky Mountain Spotted Fever Vaccine, manufactured by Lederle Laboratories Division, American Cyanamid Co. and Typhus Vaccine, Manufactured by Eli Lilly and Co. At the request of the manufacturers, the licenses for these products were revoked on June 11, 1979 and June 7, 1979, respectively.

The Panel concluded that additional data are needed for the Category IIIA drugs. The absence of such data is a material fact within the meaning of section 201(n) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(n)) and applicable regulations, § 1.21 (21 CFR 1.21). The failure to disclose a material fact would cause these drugs to be misbranded. Therefore FDA proposes to extend to viral and rickettsial vaccines the requirements in § 601.25(h)(4) that the circular and promotional material for Category IIIA drugs contain a prominent boxed statement referencing the need for further data to establish effectiveness. The boxed statement should appear in the *Indications* section of the labeling. The FDA also proposes to extend to viral and rickettsial vaccines the requirement of § 601.25(h)(5) that a written informed consent be obtained from participants in the requisite additional studies, and that participants receive an explanation of the product and the purpose of the study and a clear opportunity to refuse to participate.

d. *Category IIIB. Biological products for which available data are insufficient to classify their safety and effectiveness and should not continue in interstate commerce:* Poliovirus Vaccine, Live, Oral, Type 1, Type 2, and Type 3, Pfizer, Ltd., License No. 338; Poliomyelitis Vaccine, Cutter Laboratories, Inc., License No. 8; Poliomyelitis Vaccine (Purivax), Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Poliomyelitis Vaccine; Poliomyelitis Vaccine, Adsorbed, Parke, Davis and Co., License No. 1; Poliovirus Vaccine, Live, Oral, Trivalent, Poliovirus Vaccines, Live, Oral, Type 1, Type 2, and Type 3, (Sabin), Wyeth Laboratories, Inc., License No. 3; Smallpox Vaccine, Massachusetts Public Health Biologic Laboratories, License No. 64; Smallpox Vaccine, Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Immune Serum Globulin (Human), North American Biologicals, Inc., License No. 413; Measles Immune Globulin (Human), Lederle Laboratories Division, American Cyanamid Co., License No. 17; Measles Immune Globulin (Human), Parke, Davis and Co., License No. 1.

The Panel found that many of these products have not been manufactured for a number of years and that the only way to assure that competence currently exists for their production, and to guarantee their safety and efficacy, is to require a new submission when or if the licensee desires to resume marketing. The Panel did not receive sufficient information from Pfizer Ltd., for the monovalent poliovirus vaccines or from the producers for the human immune serum globulins, and could make no determinations regarding the relative benefits and risks of these products. The Panel recommended that the licenses be suspended or revoked pending the satisfactory completion of additional testing because there is no evidence presumptive of safety or effectiveness for the products.

The FDA agrees with the Panel's findings and recommendations concerning these drugs and, in accordance with §§ 601.5 and 601.25(f)(3), intends to publish a NOH to revoke the licenses for these products. In addition to the lack of proven safety and effectiveness with respect to Poliomyelitis Vaccine (Purivax), manufactured by Merck Sharp & Dohme, Poliomyelitis Vaccine, and Poliomyelitis Vaccine, Absorbed, manufactured by Parke, Davis and Co., and Measles Immune Globulin (Human), manufactured by Lederle Laboratories Division, American Cyanamid Co., FDA also intends to base revocation, authorized by § 601.5(b)(2), upon the fact that manufacture has discontinued to such an extent that a meaningful inspection cannot be made.

The following licenses for products in Category IIIB were revoked at each manufacturer's request and revocation proceedings are unnecessary:

Product	License No.	Manufacturer	Date of revocation
Poliovirus Live, Oral, Type 1, Type 2, and Type 3.	338	Pfizer Ltd	6/12/79
Poliomyelitis Vaccine	8	Cutter Lab., Inc.	12/28/78
Poliovirus Vaccine, Live, Oral, Trivalent (Sabin) Poliovirus Vaccine Live, Oral, Type 1, Type 2, and Type 3 (Sabin).	3	Wyeth Lab., Inc	9/06/74
Smallpox Vaccine	64	Massachusetts Public Health Biologic Laboratories.	12/22/76
Immune Serum Globulin (Human)	413	North American Biologicals Inc.	5/21/75
Measles Immune Globulin (Human)	1	parke, Davis and co.	11/4/77

North American Biologicals, Inc., transferred its manufacturing processes and facilities to Merieux Institute, Inc., Miami, FL. Merieux Institute, Inc., was issued License No. 623, on May 21, 1975, for the manufacture of Immune Serum Globulin (Human).

2. The Panel recommended that a public compensation system be established under which the government accepts; responsibility to recompense

those who suffer damages from the recognized hazards of immunication when licensed vaccines are used.

A similar recommendation concerning a public compensation system was made at the National Immunization Conference held in April 1977. The agency advises that such a public compensation system is a policy issue which is under study by the office of the Secretary, Department of Health, Education, and Welfare (DHEW). If endorsed by the Secretary, implementation of a public compensation system would require Congressional action.

3. The Panel recommended that FDA, acting through the Bureau of Biologics, rather than the Center for Disease Control (CDC) and the Advisory Committee on Immunization Practices (ACIP), should be responsible for promulgating vaccine usage recommendations.

The FDA notes, first, that ACIP now is advisory to the Assistant Secretary for Health and renamed the Immunization Practices Advisory Committee (IPAC). In addition, FDA is cognizant of the Panel's acknowledgement that "in view of the present commendable collaboration between CDC (and its IPAC appendage) and the Bureau of Biologies, the question might appear to be academic * * *." Therefore, because this interaction between the two organizations can be expected to continue, this matter is not an urgent problem at this time. Any further consideration of this issue will be referred to the Office of the Assistant Secretary for Health.

4. The Panel directed several comments to the IPAC concerning its recommendations for the use of various products. The Panel's comments will be discussed with IPAC and the preamble to final rule will advise manufacturers of their conclusions and any additional labeling revisions that may be necessary to accurately reflect PHS policy (see item 5 below).

5. The Panel recommended a number of specific labeling changes concerning manufacturers' labeling. The agency agrees with the Panel's recommendations for labeling changes. The public is invited to comment on the Panel recommendations affecting product labeling. All labeling changes concerning product use will be discussed with the IPAC and other appropriate groups (e.g., the American Academy of Pediatrics Committee on Infectious Diseases). Upon publication of the final rule, FDA will advise manufacturers when to submit appropriately revised labeling to the Bureau of Biologics for review and approval. Such proposed labeling should conform to the Panel's recommendations, as they may be modified by the final rule, and to regulations governing the content and format of labeling for human prescription drugs, as well as the procedures for requesting a waiver from certain labeling requirements, when those regulations become effective for viral and rickettsial products under review (21 CFR 201.56, 201.57, and 201.58, see the **Federal Register** of June 26, 1979 (44 FR 37434)).

6. The Panel recommended that the government study vaccines for possible subtle and/or long delayed adverse effects.

The FDA agrees that studies designed to evaluate such effects are desirable. The agency has already engaged in selected postmarket surveillance studies with other interested government agencies—the CDC, the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), and the Department of the Army. These efforts will be continued as opportunities for meaningful studies present themselves. The FDA has endorsed postmarketing surveillance in its legislative proposals, particularly the drug reform bill presented to the 95th Congress.

7. The Panel recommended that FDA consider ways of improving laboratory techniques for evaluating and updating standards for safety, potency, and effectiveness for some of the reviewed products.

Standards for determining the safety, potency, and effectiveness of viral and rickettsial vaccines are related to the current state of biomedical knowledge and technology. The existing policy of FDA encourages improvement of standards whenever sound and substantiated laboratory and clinical data demonstrate that changes in methods of production and quality control testing will result in a better product. Within this context, and noting that most of the products reviewed by this panel were found to be safe and effective, the FDA agrees with these recommendations. The agency will continue to be cognizant of new procedures which will improve standards for vaccines.

8. The Panel found that licensed viral vaccines which are safe and effective as single viral products are also safe and effective when combined with other licensed viral vaccines. Accordingly, the Panel recommended that the Bureau of Biologic's interpretation of § 610.17 (21 CFR 610.17) concerning permissible combinations of licensed products be modified to allow a licensed manufacturer to purchase and combine another licensed viral vaccine without being licensed for the purchased component vaccine(s).

The regulation on permissible combinations, § 610.17, requires that manufacturers of combination biological products be licensed for the combination product. In addition, to assure that the individual therapeutic, prophylactic, or diagnostic products of the combination product are compatible, safe, potent, and effective, it has been the agency's policy to require the manufacturer of the combination product to obtain a license for each product in the combination as well.

FDA adopts the Panel recommendation and will now permit manufacturers of combination viral vaccine(s) to purchase licensed viral vaccine(s) from another manufacturer(s) and combine them without obtaining a license for the purchased vaccine(s), provided that the manufacturer of the combination product—(1) performs laboratory and clinical studies to demonstrate compatibility, safety, potency, and effectiveness of the combination product (§ 601.2), (2) obtains a license for the combination product, and (3) identifies, in the package insert, the manufacturer of each purchased vaccine component used in the manufacture of the combination product.

9. The Panel recommended the following for both the live and the inactivated poliovirus vaccines:

(i) Research into the seed strains and the substrates used for cultivation of the virus.

(ii) Surveillance of large comparison groups of recipients of vaccines produced in diploid and in simian cell substrates.

(iii) Identification and development of better in vitro marker correlates of the neurovirulence of poliovirus strains used for the live vaccine, and application of appropriate statistical definitions for interpretation of the monkey test for neurovirulence.

(iv) Comparison testing of inactivated poliomyelitis vaccines licensed in the United States and of those used in Europe to determine their relative potency, and reevaluation of the U.S. potency standards in light of these results.

(v) Use of new methodologies, as they evolve, for the detection and elimination of adventitious agents as well as other foreign nucleic acids or proteins from the substrates used for viral vaccine production.

The Panel found, as have other expert groups, that both the live and the inactivated poliomyelitis vaccines are

safe and effective. The FDA agrees that it is important to continue to apply scientific advances to vaccine technology.

The FDA has supported and will continue to support research on cell substrates, in vitro and in vivo measures of attenuation, assays for extraneous agents and substances, and alternate strains of virus for vaccine production. As in other areas of biologics research, these efforts involve a productive interchange between FDA and other biomedical research groups in government, academia, and industry.

In cooperation with other national control authorities and the World Health Organization (WHO), FDA has for several years been involved in an analysis of data relating to neurovirulence testing of live poliovirus vaccine in primates. The testing is complex and difficult and is meaningful only insofar as results are shown to be related to predictable vaccine performance in humans. Nevertheless, it is anticipated that data analysis will ultimately serve as a basis for revising and updating the existing standards for neurovirulence interpretation both here and abroad.

A related problem not specifically addressed in the Panel report but discussed by FDA with the Panel in public sessions concerns the international shortage of primates essential for this type of testing and for the required neurovirulence testing of vaccines. In anticipation of this current shortage, FDA established domestic colonies of Rhesus monkeys. Through the funding of such activities by FDA and other HEW components, the supply of polio vacine for the United States and the availability of monkeys for vaccine testing is secure.

The FDA has already been in contact with other national control authorities, the WHO, and other interested parties regarding the need for new data relating to the comparative immunogenicity of inactivated poliomyelitis vaccines produced by differing methodologies. FDA is supporting studies that should provide information on the immunogenicity of these vaccines in humans as well as in animals. With the completion of these international comparative studies, it is possible that the resulting data will serve as a basis for modifying the labeling as well as changing potency standards for inactivated poliomyelities vaccines licensed in the United States.

FDA advises that research by the Bureau of Biologics on new methods for the detection and elimination of adventitious agents and extraneous material in substrates used for vaccine production is in progress. For example, biophysical and biochemical methods have been employed in testing for the presence of type C retroviruses; the interaction between bacteriophage and cell substrates used for vaccine production has been studied; and new systems for tumorigenicity testing of cell substrates have been developed. In addition, the Bureau is supporting extramural studies designed to detect and eliminate adventitious agents and has discussed with manufacturers research on new manufacturing methods that may improve the purity of viral vaccines.

10. Although the Panel found that all licensed smallpox vaccines currently produced are safe and effective, they recommended that the standards in 21 CFR Part 630, Subpart H, be amended, for the improvement of the quality of the product, to require—

(i) Use of the same strain of seed virus by all manufacturers;

(ii) Use of a seed lot system;

(iii) A test for potency by the pock counting method;

(iv) Sterility standards for percutaneous vaccines consistent with those currently required for jet-gun vaccines; and

(v) The elimination of viable bacterial organisms in jet-gun vaccines.

The Panel also suggested that an effort be made to detect other extraneous organisms, in addition to bacteria, in calif lymph vaccines.

The FDA agrees that these suggestions would improve the vaccine's quality. However, the greatly reduced need for smallpox vaccine resulting from the international eradication of smallpox makes it probable that manufacturers may terminate their production of vaccine rather than commit new funds to upgrade existing production methods. Therefore, the agency particularly invites comments on these recommendations, noting that the possible termination of the production of smallpox vaccine may be potentially of more concern than achieving a marginal increase in the benefit/risk ratio by moderately upgrading existing production methods.

As the Panel notes, differing degrees of documentation exist on the effectiveness of the strains of vaccine virus being used in production. Although the Panel found those smallpox vaccines currently produced to be effective, they recommended that the strain with greatest documentation of safety and effectiveness be used by all manufacturers. The FDA will explore the feasibility of such a change with those manufacturers who intend to continue to produce the vaccines.

The FDA agrees that a seed lot system should be used in the production of smallpox vaccine and invites comments on its intention to require those manufacturers continuing production to amend their product license to adopt a seed lot system.

With respect to the use of the pock counting method for potency testing, § 630.73 (21 CFR 630.73) has already been amended to require such testing (see the **Federal Register** of November 19, 1976 (41 FR 51009)).

The FDA will investigate the feasibility of requiring that vaccines meet more stringent sterility standards. The development of new tests for extraneous organisms in calf lymph vaccines and the determination of the tests' usefulness in the manufacture of smallpox vaccine will likely require a collaborative research effort between FDA and the manufacturers.

11. The Panel commented that the required testing of cell substrates for extraneous agents or indigenous viruses should be updated, especially in the duck embryo system, noting the absence of required testing for duck infectious anemia virus (DIAV).

The regulations for live rubella virus vaccine, propagated in duck embryo cell cultures, in § 630.62(b) prescribe that the embryonated eggs used as a source of the tissue for the propagation of rubella virus shall be derived from flocks certified to be free of agents pathogenic for ducks. There are similar regulations for the manufacture of measles virus vaccine, live, attenuated (§ 630.32(b)) and mumps virus vaccine, live (§ 630.52(a)). A report in the *Journal of the National Cancer Institute* (H. G. Purchase, C. Ludford, K. Nazerian and H.W. Cox, 51:489–499, 1973) identifies DIAV as a member of the reticuloendotheliosis virus (REV) group which includes REV isolated from turkeys, spleen necrosis virus isolated from ducks, and chick syncytial virus isolated from chickens. The report states that the members of the REV group are serologically indistinguishable in the fluorescent antibody test. The author noted that antibody indicative of contact with these agents occurred in white Pekin ducks only when they were in contact with wild ducks and not when reared in closed flocks under commercial conditions.

As a result of the Panel's discussions, a manufacturer of measles, mumps and rubella vaccines that are produced in avian cell cultures submitted data demonstrating that closed duck and chicken flocks, from which the embryos used for vaccine production are derived, are free of REV as evidenced by the lack of antibodies specific for those agents.

In addition, representative lots of measles, mumps, and rubella virus vaccines were tested for REV by the indirect fluorescent antibody method and were found to be free of the agents.

Nevertheless, assurances should be provided that commercial ducks have not contracted DIAV from accidental contact with wild ducks. For this reason, FDA agrees with the Panel's comments that embryonated eggs for propagating viral vaccines should be derived from flocks certified to be free of DIAV as well as any other REV organism. Since the hazard of biocontamination with agents of the REV group applies to measles and mumps virus vaccines as well, manufacturers of live virus vaccines produced in avian tissue should test birds for REV viruses before introduction into the breeding colony and periodically thereafter.

Accordingly, FDA is proposing that §§ 630.32(b), 630.52(a), and 630.62(b) be amended to require that embryonated eggs intended for manufacture of measles virus vaccine, live, attenuated, mumps virus vaccine, live, and rubella virus vaccine, live, be derived from flocks certified to be free of REV. There is no need to change the wording of § 630.52(a) because § 630.52(a) currently states that embryonated eggs for propagating mumps virus shall be derived from flocks certified or tested as prescribed in § 630.32(b).

12. The Panel recommended that the regulations concerning safety tests for rubella vaccines (§ 630.65) should specify the incubation period for the embryonated eggs before and after inoculation with virus, and the subpassage requirement of tests to be employed.

The FDA agrees with the Panel's recommendation. The tests for safety performed on live virus vaccines prior to clarification are designed to detect the presence of possible adventitious agents which may originate from the cell substrate or from personnel processing the vaccine. The tests include a variety of host systems, i.e., adult mice, suckling mice, and at least four different cell cultures as well as media for the detection of bacteria and mycoplasma. The embryonated egg is a classic host for the detection of a variety of adventitious agents and is used in addition to these host systems.

Measles virus vaccine, live, attenuated, mumps virus vaccine, live, and rubella virus vaccine, live, are produced in avian cell cultures, and similar safety tests are applied to all three vaccines. The embryonated egg safety test prescribed for rubella virus vaccine in § 630.65(a)(5) and (6) and (c)(5) and for mumps virus vaccine in § 630.55(a)(5) requires that the test shall be performed as prescribed in § 630.35(a)(5) for measles virus vaccine. Therefore, it is appropriate to specify, in § 630.35(a)(5), the incubation period and subpassage requirements that are appropriate for all three live virus vaccines, and the agency proposes to amend § 630.35(a)(5) accordingly.

The proposed requirements for the inoculation of embryonated eggs (§ 630.35(a)(5)) are based upon generally accepted methods. A description of the methods of inoculation, incubation, harvesting, and subpassaging and their application is found in "Diagnostic Procedures for Viral and Rickettsial Infections," Fourth Edition, American Public Health Association, New York, E. H. Lennette and N. J. Schmidt, Editors, 1969.

13. For influenza vaccines, the Panel recommended that (i) additional controlled trials of safety, antigenicity, and efficacy be required when a major change is introduced into the process of vaccine production, (ii) other possible tests of potency be explored, particularly animal test models and in vitro measurement for antigenic mass, (iii) standards be established for the maximal acceptable level of contaminants such as diffusable chick proteins and other foreign nonviral protein, and (iv) additional special studies be performed.

The FDA agrees with the Panel's findings that additional testing be required for influenza vaccine if major manufacturing changes are made. The establishment licensing regulations, § 601.12 (21 CFR 601.12), require manufacturers to advise FDA of major proposed changes before the changes are made. When major changes in the production of vaccine have been proposed, FDA has required manufacturers to provide experimental in vitro and in vivo data demonstrating the safety and effectiveness of the vaccine produced by the new method.

As the Panel notes, experience over the years has shown that the presence of circulating antibodies directed against the surface antigens of influenza virus generally correlates with protection against the disease. The conclusion by the Panel that the currently licensed inactivated influenza vaccines are effective is in good part based upon this established relationship between antibody levels and vaccine efficacy. The FDA agrees that when major changes in manufacturing are proposed, it is important to evaluate the safety and antigenicity of the modified product by appropriate clinical trials. Experience has shown that such studies can be completed and their results analyzed within a matter of months, making the acquisition of such data entirely practical. Compared to the evaluation of human antibody response (an indirect measure of vaccine effectiveness), the direct determination of effectiveness is far more difficult. The direct measure requires detailed virologic and epidemiologic study of both vaccinated and unvaccinated populations over an extended period of time. Since influenza may not occur or may occur only sporadically in the populations during the period of study, even a large, complex, and costly trial may fail to provide useful results. For these reasons, data of this nature have more often been provided retrospectively, and by studies supported by public funds, than prospectively by vaccine manufacturers.

The FDA believes that direct protection data should continue to be collected whenever epidemiologic circumstances suggest that a reasonable opportunity exists. As in the past, several government agencies (e.g., NIH, CDC, FDA, DOD) as well as industry will be encouraged to participate in such studies, which are best characterized as a continuing documentation rather than an absolute prelicense requirement. The collection of direct protective efficacy data by animal studies is generally feasible within a reasonable time frame. Consequently, laboratory studies in animals and clinical data relating to antigenicity are normally required of manufacturers proposing new or substantially changed inactivated influenza virus vaccines.

The FDA policy is to continually upgrade those laboratory and research techniques, including potency tests, which form the basis of FDA decisions. Several experimental parameters of influenza vaccine potency have been evaluated in vitro and in vivo in laboratory animals. Indeed, the Bureau of Biologics, working with CDC and NIAID, have performed research correlating in vitro potency determinations with antigenicity in clinical investigations and, as a result, in 1978 instituted a new in vitro procedure for assaying potency of influenza vaccines based on content of hemagglutinin.

FDA agrees with the Panel's recommendations concerning the establishment of standards for maximal acceptable levels of nonviral components in influenza vaccine. As soon as sufficient data to develop additional standards for nonviral contaminants are available and evaluated, FDA will propose standards

regarding acceptable levels of nonviral contaminants in influenza vaccines.

Additional special studies were recommended by the Panel, including (i) evaluation of safety, antigenicity and efficacy of influenza vaccines in high risk adults and children under 6 years of age; (ii) evaluation of the protective efficacy of the Type B components; (iii) review of the status of adsorbents and adjuvants in experimental influenza vaccines; and (iv) surveillance of rare but severe vaccination sequellae.

Since 1973, the Bureau of Biologics has supported clinical trials which have demonstrated that the antigenicity and reactivity of influenza vaccines are similar in high risk and normal individuals. Extensive studies evaluating the safety and antigenicity of influenza vaccines in children under 6 years of age were conducted in 1976 as part of the National Influenza Immunization Program and in 1978 with A/USSR/77 vaccines. As previously noted, due to the sporadic nature of influenza epidemics, it is difficult to evaluate field efficacy. However, one study sponsored by the Bureau of Biologics has demonstrated that both a whole and split-product influenza vaccine were protective in a high risk group of children with cystic fibrosis when they were exposed to an epidemic of A/Victoria (Gross, et al., *Journal of Infectious Diseases,* 136:623–632, 1977).

In addition, studies to monitor the benefits and risks of influenza vaccines are in progress in NIAID-sponsored clinical trails in vaccine evaluation centers throughout the United States. Other special studies will be considered as opportunities permit, and will be explored with agencies such as CDC and NIH, which also have interests and responsibilities in these matters.

Concerning the evaluation of the reactivity of the Type B component in relation to the Type A antigens, the immediate issue of the local and systemic reactivity of influenza vaccines in young children has been largely circumvented by using reduced amounts of antigen and divided vaccine dosages. Studies conducted in 1976 and 1977 demonstrated that vaccines containing two Type A antigens (A/Texas and A/USSR) and the Type B component had reactivity low enough to make them acceptable for use in young children. Additionally, field studies sponsored by NIAID to evaluate the protective effectiveness of Type B vaccines are currently in progress.

The FDA agrees that the status of adsorbents and adjuvants used in experimental influenza vaccines should be reviewed periodically. This policy is currently followed by FDA in the review of clinical studies performed under an IND and in support of license applications or amendments.

The FDA agrees that increased surveillance of rare but severe vaccination sequellae is desirable. To aid in this effort, the FDA announced in the **Federal Register** of April 24, 1979 (44 FR 24233) the availability of a proposed regulation requiring records and reports of adverse reactions and product experiences involving licensed biological products. According to the draft proposal, manufacturers of licensed biological products would be required to immediately report any severe (life threatening or fatal) reactions to the Bureau of Biologics. Copies of this draft proposal are available from the Hearing Clerk under docket number 79N–0089. The comment period on the draft proposal ended June 25, 1979.

CDC, in cooperation with the American Academy of Neurology is currently monitoring the nation-wide incidence of Guillain-Barre Syndrom (GDS). This monitoring system will help determine the relative risk of GBS from vaccinations. In addition, the CDC, by Congressional authority, maintains a general vaccine surveillance program for all Federally-supplied vaccines.

14. The Panel recommended that efforts be made to detect and, if present, eliminate extraneous microorganisms, including avian REV, which may be present in duck embryo used for the production of rabies vaccine.

A license application for rabies vaccine produced in human diploid cells is currently under review by the Bureau of Biologics. It is anticipated that the manufacture of duck embryo rabies vaccine will terminate as soon as the product is no longer needed. However, should production continue, the development of procedures for the detection and elimination of extraneous organisms will be discussed with the manufacturer.

15. The Panel expressed concerned that no avian leukosis virus (ALV)-free yellow fever vaccine is available in this country and requested that every effort be made to insure that ALV-free vaccine is made available in the United States.

The FDA is also concerned about this problem and has conducted extensive research in an effort to aid in the development and assessment of a safe and effective ALV-free yellow fever virus strain for vaccine production. These efforts have a high priority and will continue until an ALV-free vaccine is made available in this country.

16. The Panel recommended improving Rocky Mountain Spotted Fever (RMSF) vaccine and typhus fever vaccine by changing current potency standards to require a defined whole rickettsial organism content and by requiring the use of a reference preparation in the assay test to better correlate the potency for humans. In addition, the Panel recommended that the safety standards be amended to establish limits for endotoxin content and to exclude mycoplasma and other extraneous agents prior to inactiviation.

The FDA agrees with the Panel's recommendation to improve RMSF vaccine and typhus fever vaccine. However, with the revocation of Lederle's product license on June 11, 1979, there are no RMSF vaccines licensed for manufacture in the U.S. The U.S. Army Medical Research Institute on Infectious Diseases and the NIAID Rocky Mountain Laboratory are, however, conducting RMSF vaccine studies. These studies are designed to answer questions concerning potency standards, define a whole rickettsial organism content, establish limits for endotoxin content, and provide methods to exclude extraneous agents from RMSF. There has been no active effort to establish a reference RMSF vaccine. However, a reference preparation or one that closely parallels the vaccine the Army is studying will likely result when the clinical trials with the vaccine developed at the U.S. Army Medical Research Institute on Infectious Diseases are finished. The NIAID has also expressed an interest in the question of an improved RMSF vaccine. The FDA has been and will continue to be in close contact with these agencies concerning this matter. Appropriate changes in the regulations will be proposed as soon as requisite laboratory and clinical data have been obtained and reviewed.

The FDA agrees that efforts should be made to improve the potency test method for typhus vaccine, including the use of an appropriate reference, if this Category IIIA product is to continue in interstate commerce. FDA proposes to require that the manufacturers who intend to continue production of this product initiate appropriate studies in accordance with the Panel's recommendations and § 601.25(h) (21 CFR 601.25(h)).

17. The Panel recommended that efforts be made to improve immune serum globulin (ISG) by exploring the possibility of (i) replacing thimerosal as a preservative because of the possibility of sensitization, (ii) developing ISG's that can be safely and effectively administered intravenously and (iii) improving the product's stability.

The desirability of replacing thimerosal as a preservative in

biologicals is of major concern primarily with intradermally inoculated skin test products and where thimerosal-induced skin reactions may interfere with an accurate diagnostic reading. However, there is no evidence that thimerosal affects either the safety or the effectiveness of ISG, and reactions to thimerosal have presented little if any problem. There are only a few preservatives that have been found to be safe and effective for use in injectable biological products. Other substances, frequently employed as preservatives in nonbiological products, are unacceptable because of interactions with the proteinaceous components of biologicals and because they may also be sensitizing. Extensive research is therefore required to demonstrate the acceptability of any new preservative in each product. Therefore, before considering regulations proposing the replacement of thimerosal in ISG, data must be developed showing that other preservatives are safe and effective. Interested persons are invited to submit data on the safety and effectiveness of other preservatives or single dose forms of globulin products containing no preservative.

The FDA concurs with the Panel that it would be useful to have ISG which can also be safely and effectively administered intravenously (IV–ISG). There has been considerable interest and progress in this area by both the manufacturers and university-based scientists. On October 30 and 31, 1979, FDA, in conjunction with NIH, held an Immunoglobulin Workshop to discuss the characteristics and current or potential uses of immunoglobulins for intramuscular and intravenous administration, including a review of the European experiences regarding the use of IV–ISG. The information provided by this Workshop will aid interested manufacturers and FDA in developing and assessing immunoglobulin preparations suitable for intravenous administration.

The agency concurs that efforts to improve the stability of Immune Serum Globulin and other immune globulins should be pursued. The Bureau of Biologics' Division of Blood and Blood Products has performed studies to assess the stability of Immune Serum Globulin and to develop methods not only for quantitating any physicochemical deterioration of the product that occurs during the dating period, but also for predicting stability (A. M. Young, D. L. Aronson and J. S. Finlayson, " Urokinase-incubation Method for Predicting the Stability of Immune Globulin," *Journal of Biological Standardization*, 6:27–43, 1978). Studies designed to identify factors responsible for instability are continuing.

18. The Panel recommended that the indications for use of ISG included on the labeling conform to IPAC recommendations

The Bureau of Biologics has developed guidelines for the package insert for Immune Serum Globulin. On April 14, 1978, the availability of these guidelines was announced in the **Federal Register** (43 FR 15779). The recommendations of the IPAC, as well as those of other bodies such as the Committee on Infectious Diseases, American Academy of Pediatrics, were used in the development of these guidelines. All manufacturers of the product have now adopted or are in the process of adopting the guidelines. The guidelines, as well as the manufacturers' labeling, will be reviewed periodically for conformity with the best current medical practice, scientific information, and IPAC recommendations.

19. The Panel recommended that the regulations for ISG be modified to include standards for the composition of each lot in terms of quantity and characteristics of immunoglobulin-G (IgG), relative content of other immunoglobulins and of other contaminating serum proteins. Also, within the limits of applicable technology, the Panel recommended that lots of ISG should be characterized with respect to antibody titers against measles, and hepatitis-A viruses.

The agency agrees that revised regulations for ISG should include standards for the quantity and molecular characteristics of IgG, which is the major protein constituent of ISG. At present, the purity of ISG is defined on the basis of electrophoretic mobility (21 CFR 640.103(b)). When more direct methods for defining this purity in terms of IgG have been established and when appropriate limits for the purity and the molecular characteristics of the IgG can be determined, the agency will propose revised regulations that embody these changes. The issue of molecular characteristics is closely related to that of ISG stability, which is addressed in item 17 of this preamble. In general, the amount of contaminating proteins other than immunoglobulins is determined by measuring the percent of immunoglobulins and treating the remainder as contaminating proteins in a manner analogous to that used for albumin (see 21 CFR 640.82(b)). Studies by the Bureau of Biologics' Division of Blood and Blood Products have also dealt with contaminating proteins that may be present in ISG at levels too low to permit detection by protein analyses and hence can only be measured by enzymic assays. If further study supports limits for the content of these proteins in ISG, regulations including such limits will also be proposed.

As regards the establishment of standards for the relative content of immunoglobulins other than IgG, the Division of Blood and Blood Products has completed a survey of the levels of IgG, immunoglobulin A (IgA), and immunoglobulin M (IgM) in products submitted for release by the Bureau of Biologics. The results of this survey show that these levels were relatively constant among different lots prepared by various manufacturers and were virtually the same as those reported in 1967 (Heiner, D. C. and L. Evans, "Immunoglobulins and Other Proteins in Commercial Preparations of Gamma Globulin", *Journal of Pediatrics*, 70:820–827, 1967). Because of this consistency and the expense that would be incurred if these analyses were performed on all lots, the agency does not intend to propose regulations for the relative contents of IgA and IgM. The agency, however, invites the submission of data concerning the effect of IgA and IgM content on the safety and effectiveness of ISG.

As regards antibody testing of ISG, the agency has taken note of a variety of situations in which specific antibody testing is useful. The required testing of globulins for measles antibodies is illustrative of these. The test has utility in (1) providing the user with a product that contains an amount of antibody known to be effective for the prevention or modification of natural measles; (2) providing a general indication that individual ISG lots contain the expected level of antibodies widely distributed in the population; and (3) providing a means of monitoring an antibody level that conceivably might change as a result of alterations in the epidemiology of the disease and the extensive use of vaccines. In addition to tests for measles antibodies, the regulations currently require that each lot of final product be tested for levels of diphtheria and poliomyelitis antibodies (21 CFR 640.104(a)).

For many years ISG has been widely used for the prevention of hepatitis A. In addition to specific studies cited in the Panel Report, general experience has indicated that ISG preparations prepared from large plasma pools are effective for this purpose. The requirement that ISG lots be prepared from plasma pooled from a large number of donors is based in part on the premise that such preparations will include

plasma from an adequate number of persons with antibodies to hepatitis A virus (HAV) to assure that the final product consistently contains comparable levels of such antibodies. A test has recently been developed and shown to be useful for measuring antibodies to HAV in ISG. As expected, the antibody levels observed in ISG preparations tested thus far confirm that all contain antibody and the titers fall within a relatively narrow range. These observations are consistent with the considerations mentioned above (the size of donor pools used and the experience suggesting that the ISG appears to be generally effective for immunoprophylaxis of hepatitis A). However, a minimum effective level of antibody for prevention of hepatitis A has not been established. The Bureau of Biologics is currently involved in activities which are expected to be useful in making decisions about the need for HAV antibody standards. These include: (1) measurement of levels of antibody to HAV in representative lots of ISG currently being produced and from past years; (2) preparation of a reference hepatitis A immune globulin to be used as a standard; and (3) work in experimental animal models to determine the effectiveness of ISG preparations of varying antibody content. The agency invites comments on both the appropriate tests and the minimum antibody levels to be met. The FDA intends to publish a proposal covering the specific antibody tests to be applied to ISG.

At this time the agency does not plan to require the inclusion of the antimeasles antibody level on ISG labeling. Manufacturers are currently required to determine the level of antimeasles antibody in each lot of ISG, which may be no less than the minimum effective level set by FDA (21 CFR 640.140 (a) and (b)(2)). Therefore, requiring the inclusion of the assay results on the labeling would provide little meaningful information. It seems likely that the same considerations would apply if measurement of anti-HAV antibody levels becomes a requirement.

20. The Panel found vaccinia immune globulin (VIG) to be a safe and effective product but noted that this product is no longer being produced. This is of concern to the Panel because there is a well-defined, albeit infrequent, need for VIG. The Panel therefore requested that the manufacturers reconsider their decision to discontinue the production of VIG.

The FDA notes the Panel's concern regarding the availability of VIG. Accordingly, the Bureau of Biologics will review this matter with CDC, NIH, DOD and, as appropriate, the licensed manufacturers to assess the degree of need for VIG and to determine what steps might be taken to continue the availability of VIG.

Additional background data, information, and references on which the agency relies in this proposal may be seen in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

The FDA has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)), and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 701-706)), and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Parts 601 and 630 of Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

a. In Part 601, by revising § 601.25(h) (4) and (5) to read as follows:

§ 601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

* * * * *

(h) *Additional studies and labeling.* * * *

(4) Labeling and promotional material for Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency," Skin Test Antigens, and Viral and Rickettsial Vaccines requiring additional studies shall bear a box statement in the following format:

> Based on a review by the Panel on Review of (insert name of appropriate panel) and other information, the Food and Drug Administration has directed that further investigation be conducted before this product is determined to be fully effective for the labeled indication(s).

(5) A written informed consent shall be obtained from participants in the requisite additional studies for Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency," Skin Test Antigens, and Viral and Rickettsial Vaccines explaining the nature of the product and the investigation. The explanation shall consist of such disclosure and be so made that intelligent and informed consent be given, and that a clear opportunity to refuse is presented.

* * * * *

b. In Part 630:

1. By revising § 630.32(b) to read as follows:

§ 630.32 Manufacture of live attenuated Measles Virus Vaccine.

* * * * *

(b) *Virus propagated in chick embryo tissue culture.* Embryonated chicken eggs used as the source of chick embryo tissue for the propagation of measles virus shall be derived from flocks certified to be free of Salmonella pullorum, avian tuberculosis, fowl pox, Rous sarcoma, avian leucosis, reticuloendotheliosis virus, and other adventitious agents pathogenic for chickens. If eggs are procured from flocks that are not so certified, tests shall be performed to demonstrate freedom of the vaccine from such agents. (See § 630.35(a)(8) for test of avian leucosis.)

* * * * *

2. By revising § 630.35(a)(5) to read as follows:

§ 630.35 Test for safety.

(a) * * *

(5) *Inoculation of embryonated chicken eggs.* A volume of virus suspension of each undiluted virus pool, equivalent to at least 100 doses or 10 milliliters, whichever represents a greater volume, after neutralization of the measles virus by a high titer antiserum of nonhuman, nonsimian, nonavian origin shall be tested as follows:

(i) Embryonated eggs, 10 to 11 days old, shall be inoculated by the allantoic route using 0.5 milliliter per egg. Following incubation at 35° C for 72 hours, the allantoic fluids shall be harvested, pooled and subpassed by the same route into fresh embryonated eggs, 10 to 11 days old, using 0.5 milliliter per egg and incubated at 35° C for 72 hours. Both the initial pool and the subpassage harvest shall be tested for the presence of hemagglutinin. The virus pool is satisfactory if the embryos appear normal and there is no evidence of hemagglutinating agents.

(ii) Embryonated eggs, 6 to 7 days old, shall be inoculated by the yolk sac route using 0.5 milliliter per egg. Following

incubation at 35° C for at least 9 days, the yolk sacs shall be harvested and pooled. A 10-percent suspension of yolk sacs shall be subpassed by the same route into fresh embryonated eggs, 6 to 7 days old, using 0.5 milliliter of inoculum per egg and incubated at 35° C for at least 9 days. The virus pool is satisfactory if the embryos in both the initial test and the subpassage appear normal.

* * * * *

3. By revising § 630.62(b) to read as follows:

§ 630.62 Production.

* * * * *

(b) *Virus propagated in duck embryo tissue cell cultures.* Embryonated duck eggs used as a source of duck embryo tissue for the propagation of rubella virus shall be derived from flocks certified to be free of avian tuberculosis, the avian leucosis-sarcoma group of viruses, reticuloendotheliosis virus, and other agents pathogenic for ducks. Only ducks so certified and in overt good health and which are maintained in quarantine shall be used as a source of duck embryo tissue used in the propagation of rubella virus. Ducks in the quarantined flock that die shall be necropsied and examined for evidence of significant pathologic lesions. If any such signs or pathologic lesions are observed, eggs from that flock shall not be used for the manufacture of Rubella Virus Vaccine, Live. Control vessels shall be prepared, observed and tested as prescribed in § 630.32(f).

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Interested persons may, on or before July 14, 1980 submit to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: March 30, 1980.

Jere E. Goyan,

Commissioner of Food and Drugs.

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